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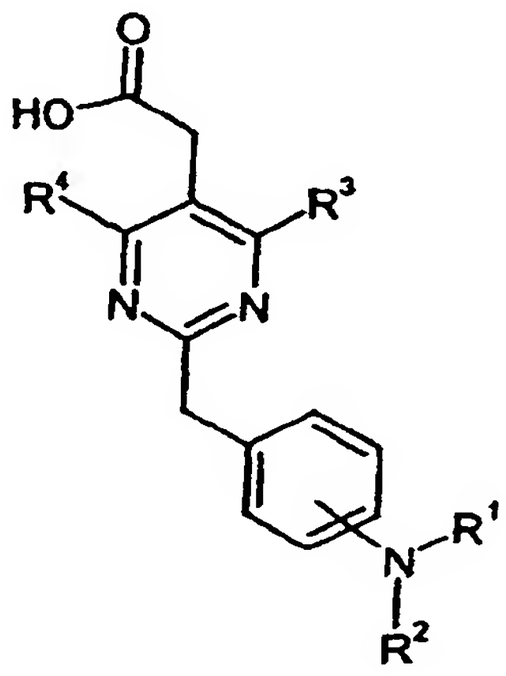
(54) Pyrimidinylacetic acid derivatives useful for the treatment of diseases mediated by CRTH2

(57) The present invention relates to a pyrimidinylacetic acid derivative of formula (1)



(I)

wherein
R^1-R^4 is defined herein, and salts thereof which is useful as an active ingredient of pharmaceutical preparations. The pyrimidinylacetic acid derivative of the present invention has excellent CRTH2 (G-protein-coupled chemoattractant receptor, expressed on Th2 cells) antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with CRTH2 activity, in particular for the treatment of allergic diseases, such as ashtma, allergic rhinitis and allergic conjunctivitis; eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis; and basophil-related diseases, such as basophilic leukemia, chronic urticaria and basophilic leukocytosis in human and other mammals.

EP 1 471 057 A1

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Description

DETAILED DESCRIPTION OF INVENTION

TECHNICAL FIELD

[0001] The present invention relates to a pyrimidinylacetic acid derivative which is useful as an active ingredient of pharmaceutical preparations. The pyrimidinylacetic acid derivative of the present invention has CRTH2 (G-protein-coupled chemoattractant receptor, expressed on Th2 cells) antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with CRTH2 activity, in particular for the treatment of allergic diseases, such as asthma, allergic rhinitis and allergic conjunctivitis; eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis; and basophil-related diseases, such as basophilic leukemia, chronic urticaria and basophilic leukocytosis in human and other mammals.

BACKGROUND ART

[0002] CRTH2 is a G-protein-coupled chemoattractant receptor, expressed on Th2 cells (Nagata et al. J. Immunol., 162, 1278-1286, 1999), eosinophils and basophils (Hirai et al., J. Exp. Med., 193, 255-261, 2001).

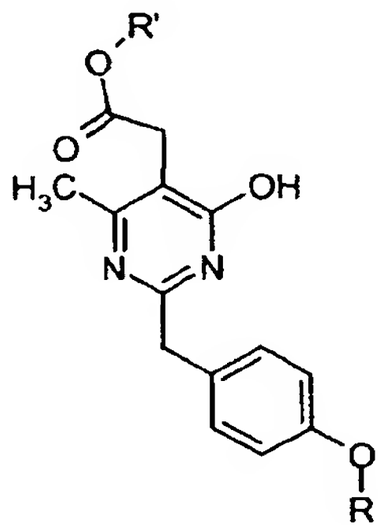
[0003] Th2-polarization has been seen in allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis (Romagnani S. Immunology Today, 18, 263-266, 1997; Hammad H. et al., Blood, 98, 1135-1141, 2001). Th2 cells regulate allergic diseases by producing Th2 cytokines, such as IL-4, IL-5 and IL-13 (Oriss et al., J. Immunol., **162,** 1999-2007, 1999; Viola et al., Blood, **91**, 2223-2230, 1998; Webb et al., J. Immunol., **165,** 108-113, 2000; Dumont F.J., Exp. Opin. Ther. Pat., **12**, 341-367, 2002). These Th2 cytokines directly or indirectly induce migration, activation, priming and prolonged survival of effector cells, such as eosinophils and basophils, in allergic diseases (Sanz et al., J. Immunol., **160**, 5637-5645, 1998; Pope et al., J. Allergy Clin. Immunol., **108,** 594-601, 2001; Teran L. M., Clin. Exp. Allergy, **29,** 287-290, 1999).

[0004] PGD_2, a ligand for CRTH2, is produced from mast cells and another important effector cells in allergic diseases (Nagata et al., FEBS Lett. **459,** 195-199, 1999; Hirai et al., J. Exp. Med., **193**, 255-261, 2001). PGD_2 induces migration and activation of Th2 cells, eosinophils, and basophils, via CRTH2 (Hirai et al., J. Exp. Med., **193,** 255-261, 2001; Gervais et al., J. Allergy Clin. Immunol., 108, 982-988, 2001; Sugimoto et al., J. Pharmacol. Exp. Ther., **305,** (1), 347-52, 2003).

[0005] Therefore, antagonists which inhibit the binding of CRTH2 and PGD_2 should be useful for the treatment of allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis.

[0006] In addition, several experimental evidence has demonstrated the contribution of eosinophils in sinusitis (Hamilos et al., Am. J. Respir. Cell and Mol. Biol., 15, 443-450, 1996; Fan et al., J. Allergy Clin. Immunol., **106,** 551-558, 2000), and Churg-Strauss syndrome (Coffin et al., J. Allergy Clin. Immunol., 101, 116-123, 1998; Kurosawa et al., Allergy, **55,** 785-787, 2000). In the tissues of these patients, mast cells can be observed to be colocalized with eosinophils (Khan et al., J. Allergy Clin. Immunol., **106,** 1096-1101, 2000). It is suggested that PGD_2 production from mast cells induces the recruitment of eosinophils. Therefore, CRTH2 antagonists are also useful for the treatment of other eosinophil-related diseases such as Churg-Strauss syndrome and sinusitis. CRTH2 antagonists can also be useful for the treatment of some basophil-related diseases such as basophilic leukemia, chronic urticaria and basophilic leukocytosis, because of high expression of CRTH2 on basophils.

[0007] Ordukhanyan, A. A et al. discloses the synthesis of pyrimidine derivative represented by the general formula:



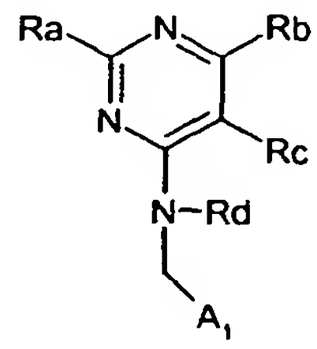
wherein

R = alkyl

R' = H or alkyl

as an intermediate for the preparation of antineoplastic agent (Khimiko-Farmatsevticheskii Zhurnal (1979), 13(9), 36-40).

[0008] GB2262096 discloses pyrimidine derivative represented by the general formula:



wherein

A_1, Ra, Rb, Rc, and Rd are defined in the application,

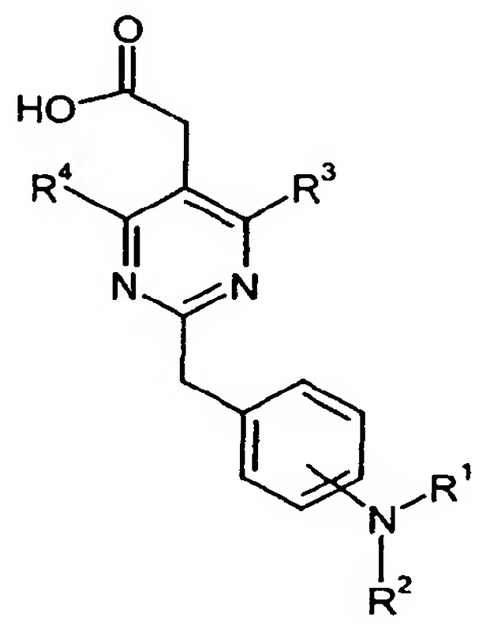
as an angiotensin II antagonist.

[0009] However, none of the references and other reference discloses pyrimidinylacetic acid derivatives having CRTH2 antagonistic activity.

[0010] The development of a compound, which has effective CRTH2 antagonistic activity and can be used for the prophylaxis and treatment of diseases associated with CRTH2 activity, has been desired.

SUMMARY OF THE INVENTION

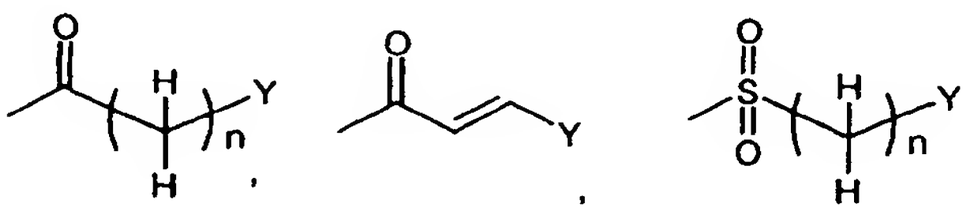
[0011] This invention is to provide a pyrimidinylacetic acid derivative of the formula (I), their tautomeric and stereoisomeric form, and salts thereof:

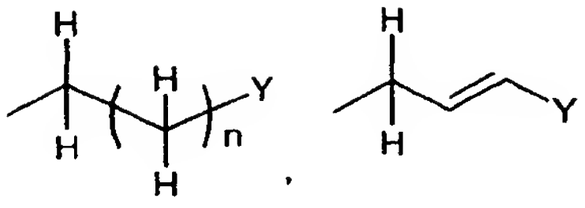


(I)

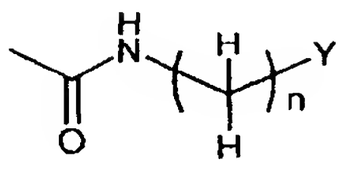
wherein

R^1 represents





or



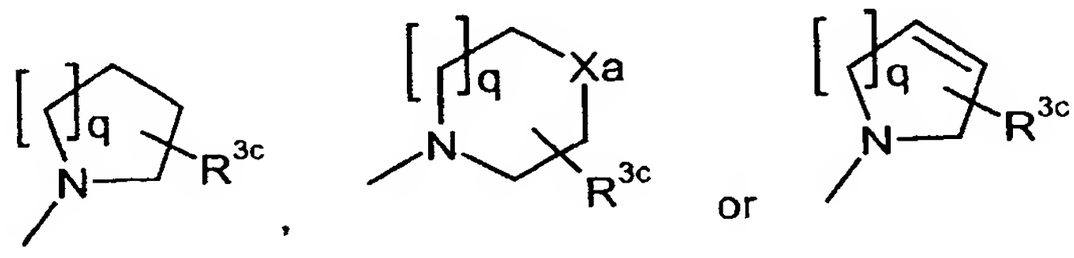
in which

n represents an integer of 0 to 6;

Y represents hydrogen, C_{3-8} cycloalkyl optionally substituted by C_{1-6} alkyl or C_{3-8} cycloalkyl fused by benzene, aryl or heteroaryl, wherein said aryl and heteroaryl are optionally substituted at a substitutable position with one or more substituents selected from the group consisting of cyano, halogen, nitro, guanidino, pyrrolyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, phenyloxy, phenyl, amino, C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen and C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen, or aryl fused by 1,3-dioxolane;

R^2 represents hydrogen or C_{1-6} alkyl;

R^3 represents C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen,



or

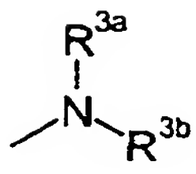
q represents an integer of 1 to 3;

R^{3c} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy or (phenyl-substituted C_{1-6} alkyl)carbamoyl;

Xa represents -O-, -S- or -N(R^{3d})-
in which

R^{3d} represents C_{1-6} alkyl;

or



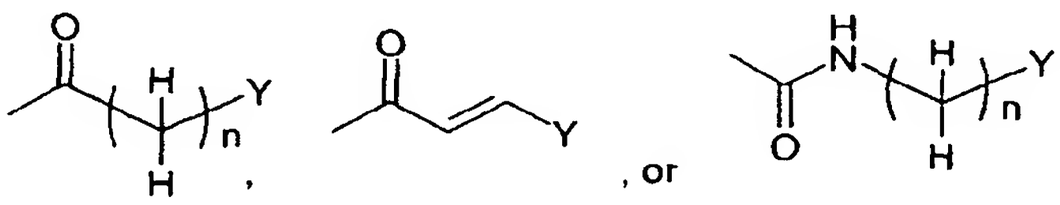
in which

R^{3a} and R^{3b} independently represent C_{3-8} cycloalkyl, or C_{1-6} alkyl optionally substituted by carboxy, C_{3-8} cycloalkyl, carbamoyl, C_{1-6} alkylcarbamoyl, aryl-substituted C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, C_{3-8} cycloalkylcarbamoyl, C_{3-8} heterocyclocarbonyl, (C_{1-6}) alkylamino, di(C_{1-6})alkylamino or C_{1-6} alkoxy; or

R^4 represents hydrogen, halogen, C_{1-6} alkoxy, di(C_{1-6} alkyl)amino, C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen.

[0012] In one embodiment, compounds of the formula (I) are those wherein:

R^1 represents



in which

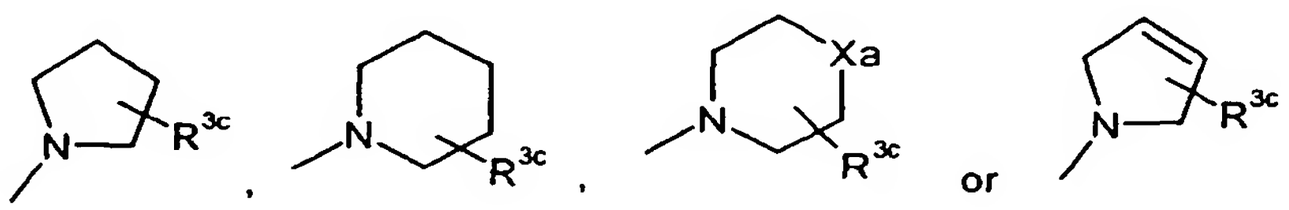
n represents an integer of 0 to 2;

Y represents C_{3-8} cycloalkyl optionally substituted by C_{1-6} alkyl, C_{3-8} cycloalkyl fused by benzene, aryl selected from the group consisting of phenyl and naphthyl, or heteroaryl selected from the group consisting of indolyl, quinolyl, benzofuranyl, furanyl and pyridyl, wherein said aryl and heteroaryl are optionally substituted at a substitutable position with one or more substituents selected from the group consisting of cyano, halogen, nitro, pyrrolyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, phenyloxy, phenyl, C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoylamino, carbamoyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen and C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen; or

R^2 represents hydrogen.

[0013] In another embodiment, compounds of the formula (I) are those wherein:

R^3 represents C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen,

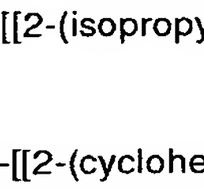


R^{3c} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy or (phenyl-substituted C_{1-6} alkyl)carbamoyl,

Xa represents -O-, -S- or -N(R^{3d})-
in which

R^{3d} represents C_{1-6} alkyl,

or



in which

R^{3a} and R^{3b} independently represent C_{1-6} alkyl optionally substituted by carboxy, C_{3-8} cycloalkyl, carbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, C_{3-8} cycloalkylcarbamoyl, C_{3-8} heterocyclocarbonyl, (C_{1-6}) alkylamino, di(C_{1-6})alkylamino or C_{1-6} alkoxy.

[0014] The preferable compounds of the present invention are as follows:

[4-methyl-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-4-methyl-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]pyrimidin-5-yl}acetic acid;

{4-chloro-6-{methyl[2-oxo-2-(1-pyrrolidinyl)ethyl]amino}-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(isopropylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

14-chloro-6-[[2-(cyclohexylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

(4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(3-phenylpropanoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

(4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(2-quinolinylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino)-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

{4-chloro-2-{4-[(4-chlorobenzoyl)amino]benzyl}-6-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(4-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(4-methylbenzoyl)amino]benzyl}-5-pyrimidinyl} acetic acid;

{2-{4-[(1-benzofuran-2-ylcarbonyl)amino]benzyl}-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(1H-indol-2-ylcarbonyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

{4-chloro-2-{4-[(4-cyanobenzoyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(2,3-dihydro-1H-inden-2-ylacetyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(3-phenoxyphenyl)acetyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(2-quinolinylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[4-chloro-6-(dimethylamino)-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-chlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(4-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[4-chloro-6-(dimethylamino)-2-(4-{[4-(dimethylamino)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-6-(dimethylamino)-2-(4-{[4-(trifluoromethyl)benzoyl]amino}benzyl)-5-pyrimidinyl] acetic acid;

[4-chloro-2-(4-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}benzyl)-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[2-{4-[(4-bromobenzoyl)amino]benzyl}-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(2,5-dichlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-difluorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,5-dichlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3-chlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(3-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[2-(4-{[(4-tert-butylcyclohexyl)carbonyl]amino}benzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-phenoxybenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-isopropoxybenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-6-(1-pyrrolidinyl)-2-(4-{[4-(1H-pyrrol-1-yl)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-methoxy-3-nitrobenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-methoxy-3,5-dimethylbenzoyl)amino]benzyl}}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

{4-{methyl[2-oxo-2-(1-pyrrolidinyl)ethyl]amino-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

[4-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[2-{4-[(4-chlorobenzoyl)amino]benzyl} -4-(dimethylamino)-5-pyrimidinyl]acetic acid;

(4-(dimethylamino)-2-{4-[(4-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-4-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-(dimethylamino)-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[2-(4-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}benzyl)-4-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-(dimethylamino)-2-(4-{[4-(trifluoromethyl)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[2-{4-[(4-bromobenzoyl)amino]benzyl}-4-(dimethylamino)-5-pyrimidinyl]acetic acid;

{4-chloro-6-[cyclohexyl(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[isopropyl(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[(2-methoxyethyl)(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

{4-chloro-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

[4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-piperidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(1H-indol-6-ylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

{4-chloro-6-methoxy-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-(2,5-dihydro-1H-pyrrol-1-yl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[ethyl(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-(3-hydroxy-1-pyrrolidinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

[4-chloro-2-(4-{[4-(methylthio)benzoyl]amino}benzyl)-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3-chloro-4-methoxybenzoyl)amino]benzyl} -6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{2-[4-(benzoylamino)benzyl]-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl} acetic acid;

{4-chloro-2-{4-[(cyclohexylacetyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl} acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(4-methylphenyl)acetyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(1-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(4-phenoxyphenyl)acetyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-dimethoxybenzoyl)amino]benzyl} -6-(dimethylamino)-5-pyrimidinyl]acetic acid;

{4-chloro-6-(dimethylamino)-2-[3-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

[4-chloro-2-{4-[(4-nitrobenzoyl)amino]benzyl} -6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[2-(4-{[4-(acetylamino)benzoyl]amino}benzyl)-4-chloro-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{2-[4-(benzoylamino)benzyl]-4-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl} acetic acid;

(4-(dimethylamino)-2-{4-[(2-quinolinylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

(4-(dimethylamino)-2-{4-[(3-methoxybenzoyl)amino]benzyl} -5-pyrimidinyl)acetic acid;

[2-{4-[(3-chlorobenzoyl)amino]benzyl} -4-(dimethylamino)-5-pyrimidinyl]acetic acid;

N-{S-(carboxymethyl)-6-chloro-2-[4-(2-naphthoylamino)benzyl]-4-pyrimidinyl}-N-methylglycine;

{4-chloro-6-(diethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

1-{5-(carboxymethyl)-6-chloro-2-(4-(2-naphthoylamino)benzyl]-4-pyrimidinyl}-L-proline;

{2-{4-[(anilinocarbonyl)amino]benzyl}-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl} acetic acid;

{2-(4-{[(benzylamino)carbonyl]amino}benzyl)-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-({[(2-phenylethyl)amino]carbonyl}amino)benzyl]-5-pyrimidinyl}acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(2-naphthylamino)carbonyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

{4,6-bis(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

[4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-6-(1-piperidinyl)-5-pyrimidinyl]acetic acid;

{4-(dimethylamino)-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

and their tautomeric and stereoisomeric form, and salts thereof.

[0015] The pyrimidinylacetic acid derivative of the formula (I) shows excellent CRTH2 antagonistic activity. They are, therefore, suitable especially for the prophylaxis and treatment of diseases associated with CRTH2 activity.

[0016] More specifically, the pyrimidinylacetic acid derivative of the formula (I) are effective for the treatment or prevention of allergic diseases such as asthma, allergic rhinitis, atopic dermatitis and allergic conjunctivitis.

[0017] Compounds of the formula (I) are also useful for the treatment or prevention of diseases such as Churg-Strauss syndrome, sinusitis, basophilic leukemia, chronic urticaria and basophilic leukocytosis, since such diseases

are also related to CRTH2 activity.

[0018] Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

[0019] The Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylamino, alkylaminocarbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl, alkoxycarbonylamino and alkanoylamino represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

[0020] Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, iso-propoxy, tert-butoxy, n-pentoxy and n-hexoxy.

[0021] Alkanoyl illustratively and preferably represents acetyl and propanoyl.

[0022] Alkylamino represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

[0023] Alkylaminocarbonyl or alkylcarbamoyl represents an alkylaminocarbonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylamino-carbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, N,N-dimethylaminocarbonyl, N,N-diethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, N-methyl-N-n-propylaminocarbonyl, N-isopropyl-N-n-propylaminocarbonyl, N-t-butyl-N-methylaminocarbonyl, N-ethyl-N-n-pentylamino-carbonyl and N-n-hexyl-N-methylaminocarbonyl.

[0024] Alkylaminosulphonyl represents an alkylaminosulphonyl radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylaminosulphonyl, ethylaminosulphonyl, n-propylaminosulphonyl, isopropylaminosulphonyl, tert-butylaminosulphonyl, n-pentylaminosulphonyl, n-hexyl-aminosulphonyl, N,N-dimethylaminosulphonyl, N,N-diethylaminosulphonyl, N-ethyl-N-methylamino-sulphonyl, N-methyl-N-n-propylaminosulphonyl, N-isopropyl-N-n-propylaminosulphonyl, N-t-butyl-N-methylaminosulphonyl, N-ethyl-N-n-pentylamino-sulphonyl and N-n-hexyl-N-methylaminosulphonyl.

[0025] Alkylsulphonylamino illustratively and preferably represents methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, tert-butylsulphonylamino, n-pentylsulphonylamino and n-hexyl-sulphonylamino.

[0026] Alkoxycarbonyl illustratively and preferably represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl. Alkoxycarbonylamino illustratively and preferably represents methoxycarbonylamino, ethoxycarbonylamino, n-propoxycarbonylamino, isopropoxycarbonylamino, tert-butoxycarbonylamino, n-pentoxycarbonylamino and n-hexoxycarbonylamino.

[0027] Alkanoylamino illustratively and preferably represents acetylamino and ethylcarbonylamino.

[0028] Cycloalkyl per se and in cycloalkylamino and in cycloalkylcarbonyl represents a cycloalkyl group having generally 3 to 8 and preferably 5 to 7 carbon atoms, illustratively and preferably representing cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0029] Cycloalkylamino represents a cycloalkylamino radical having one or two (independently selected) cycloalkyl substituents, illustratively and preferably representing cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and cycloheptylamino.

[0030] Cycloalkylcarbonyl illustratively and preferably represents cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and cycloheptylcarbonyl.

[0031] Aryl per se and in arylamino and in arylcarbonyl represents a mono- to tricyclic aromatic carbocyclic radical having generally 6 to 14 carbon atoms, illustratively and preferably representing phenyl, naphthyl and phenanthrenyl.

[0032] Arylamino represents an arylamino radical having one or two (independently selected) aryl substituents, illustratively and preferably representing phenylamino, diphenylamino and naphthylamino.

[0033] Arylcarbonyl illustratively and preferably represents phenylcarbonyl and naphthylcarbonyl.

[0034] Heteroaryl per se and in heteroarylamino and heteroarylcarbonyl represents an aromatic mono- or bicyclic radical having generally 5 to 10 and preferably 5 or 6 ring atoms and up to 5 and preferably up to 4 hetero atoms selected from the group consisting of S, O and N, illustratively and preferably representing thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

[0035] Heteroarylamino represents an heteroarylamino radical having one or two (independently selected) heteroaryl substituents, illustratively and preferably representing thienylamino, furylamino, pyrrolylamino, thiazolylamino, oxazolylamino, imidazolyl-amino, pyridylamino, pyrimidylamino, pyridazinylamino, indolylamino, indazolylamino, benzofuranylamino, benzothiophenylamino, quinolinyl-amino, isoquinolinylamino.

[0036] Heteroarylcarbonyl illustratively and preferably represents thienylcarbonyl, furylcarbonyl, pyrrolylcarbonyl, thiazolylcarbonyl, oxazolylcarbonyl, imidazolylcarbonyl, pyridylcarbonyl, pyrimidylcarbonyl, pyridazinylcarbonyl, indolyl-

carbonyl, indazolylcarbonyl, benzofuranylcarbonyl, benzothiophenylcarbonyl, quinolinylcarbonyl, isoquinolinylcarbonyl.

[0037] Heterocyclyl per se and in heterocyclylcarbonyl represents a mono- or polycyclic, preferably mono- or bicyclic, nonaromatic heterocyclic radical having generally 4 to 10 and preferably 5 to 8 ring atoms and up to 3 and preferably up to 2 hetero atoms and/or hetero groups selected from the group consisting of N, O, S, SO and SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two hetero atoms selected from the group consisting of O, N and S, such as illustratively and preferably tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

[0038] Heterocyclylcarbonyl illustratively and preferably represents tetrahydrofuran-2-carbonyl, pyrrolidine-2-carbonyl, pyrrolidine-3-carbonyl, pyrrolinecarbonyl, piperidinecarbonyl, morpholinecarbonyl, perhydroazepinecarbonyl.

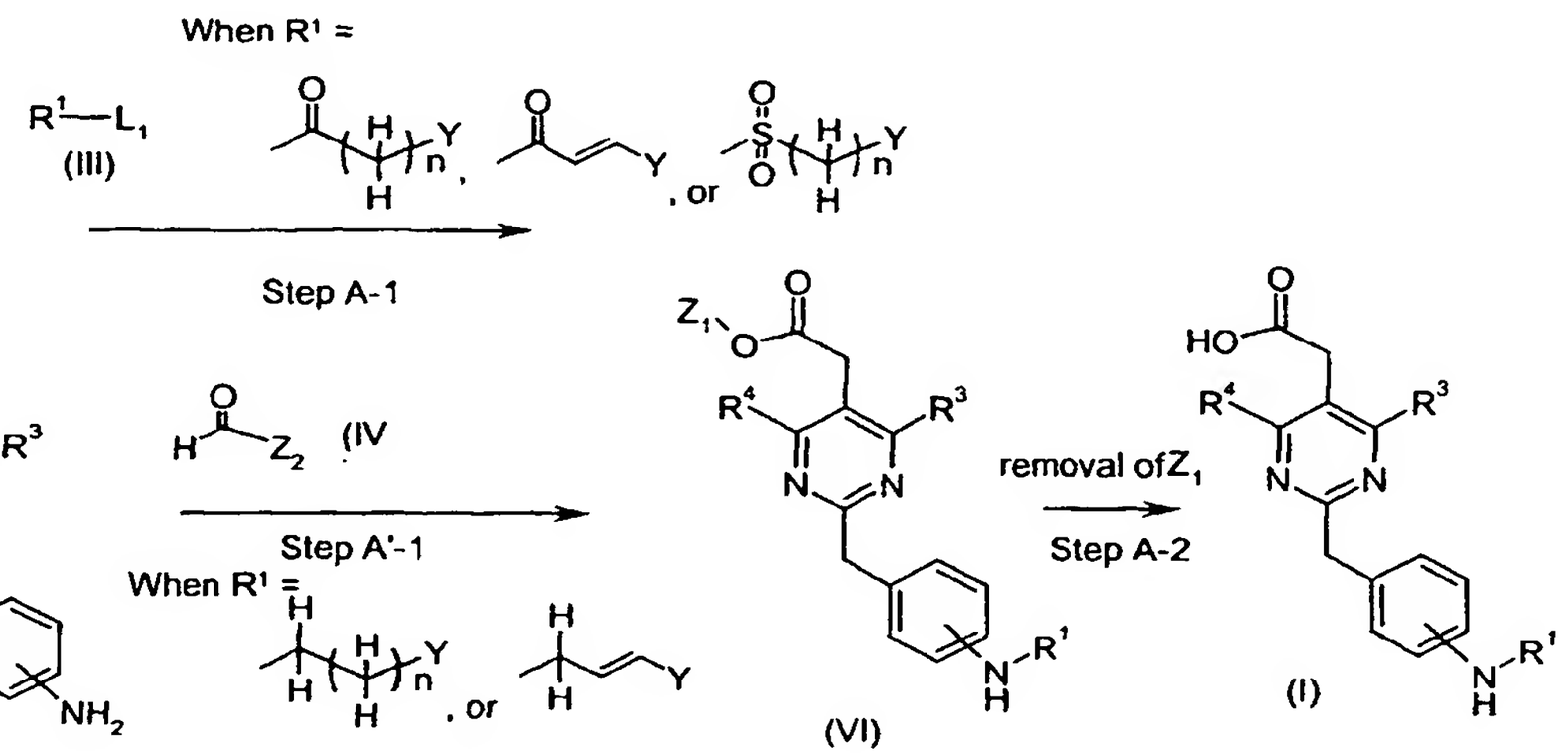
EMBODIMENT OF THE INVENTION

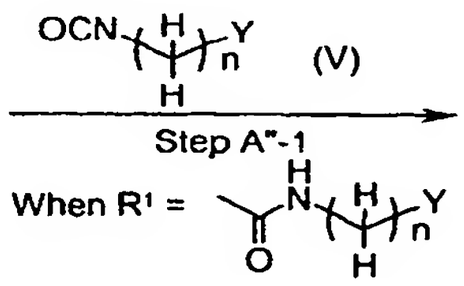
[0039] Compounds of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

[0040] Compounds of the formula (I) of the present invention can be, but not limited to be, prepared by the Method [A], [B] or [C] below.

[Method A]

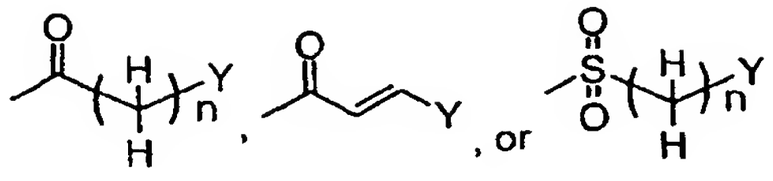
[0041]



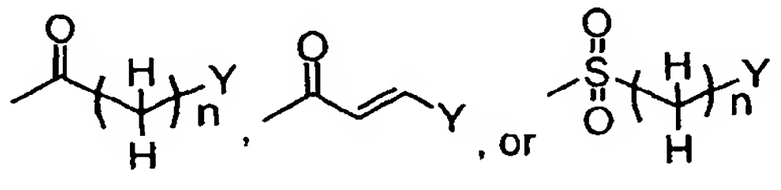


[0042] Compounds of the formula (I) (wherein R^1, R^3 and R^4 are the same as defined above) can be , for instance, prepared by the following procedures in two steps.

[0043] When R^1 is



(wherein n and Y are the same as defined above), compounds of the formula (VI) (wherein R^3 and R^4 are the same as defined above and Z_1 is C_{1-6} alkyl, benzyl, 4-methoxybenzyl or 3,4-dimethoxybenzyl) can be prepared by the reaction of compounds of the formula (II) (wherein R^3, R^4 and Z_1 are the same as defined above) with compounds of the formula (III) (wherein R^1 is



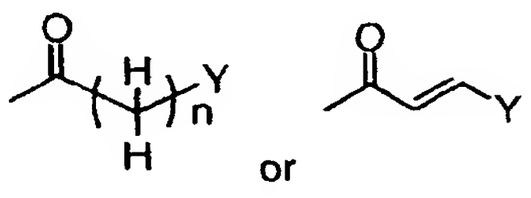
in which n and Y are the same as defined above and L_1 represents a leaving group including, for instance, halogen atom such as chlorine, bromine and iodine atom, azole such as imidazole and triazole, and hydroxy) as shown in Step A-1.

[0044] The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

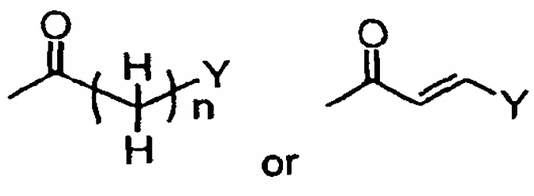
[0045] The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

[0046] The reaction can be advantageously conducted in the presence of a base including, for instance, sodium carbonate, potassium carbonate, pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, and others.

[0047] In the case L_1 in compounds of the formula (III) (wherein R^1 is



in which n and Y are the same as defined above) represents hydroxy, compounds of the formula (VI) (wherein R^3, R^4 and Z_1 are the same as defined above and R^1 is



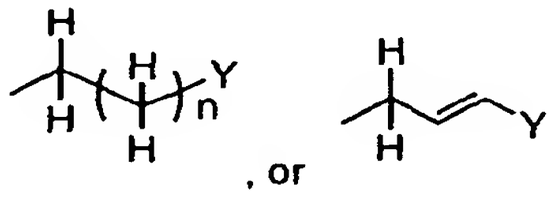
in which n and Y are the same as defined above) can be prepared by the reaction of compounds of the formula (II) (wherein R^3, R^4 and Z_1 are the same as defined above) with compounds of the formula (III) using a coupling agent including, for instance, carbodiimides such as N, N-dicyclohexylcarbodiimide and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), diphenylphosphoryl azide. N-hydroxysuccinimide, 1-hydroxybenzotiazole monohydrate (HOBt), and the like can be used as an accelerator of the reaction.

[0048] The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichlo-

romethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

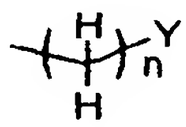
[0049] The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

[0050] When R^1 is

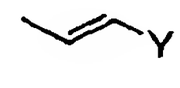


, or

(wherein n and Y are the same as defined above), compounds of the formula (VI) (wherein R^3, R^4 and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (II) (wherein R^3, R^4 and Z_1 are the same as defined above) with compounds of the formula (IV) (wherein Z_2 is



, or



,

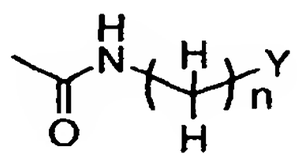
in which n and Y are the same as defined above) using a reducing agent such as sodium triacetoxyborohydride, as shown in Step A'-1.

[0051] The reaction can be advantageously conducted in the presence of a Lewis acid such as acetic acid or hydrochloric acid, or a dehydrating agent such as molecular sieves.

[0052] The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as 1,2-dichloroethane, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

[0053] The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

[0054] When R^1 is



(wherein n and Y are the same as defined above), compounds of the formula (VI) (wherein R^3, R^4 and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (II) (wherein R^3, R^4 and Z_1 are the same as defined above) with compounds of the formula (V) (wherein n and Y are the same as defined above) as shown in Step A"-1.

[0055] The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

[0056] The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

[0057] In Step A-2, compounds of the formula (I) (wherein R^1, R^3 and R^4 are the same as defined above) can be prepared by the removal of protective group Z_1 of compounds of the formula (VI) (wherein R^1, R^3, R^4 and Z_1 are the same as defined above).

[0058] The removal of protective group Z_1 can be conducted by using a base including, for instance, sodium hydroxide, lithium hydroxide and potassium hydroxide, or an acid including, for instance, HCl, HBr, trifluoroacetic acid and BBr_3. The deprotection can also be done by hydrogenation using a catalyst including, for instance, palladium on carbon and palladium hydroxide, when Z_1 is benzyl , 4-methoxybenzyl or 3,4-dimethoxybenzyl. Also, the deprotection can be done by using a reagent such as ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), when Z_1 is 4-methoxybenzyl or 3,4-dimethoxybenzyl.

[0059] The reaction can be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), sulfoxides such as dimethylsulfoxide (DMSO), alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

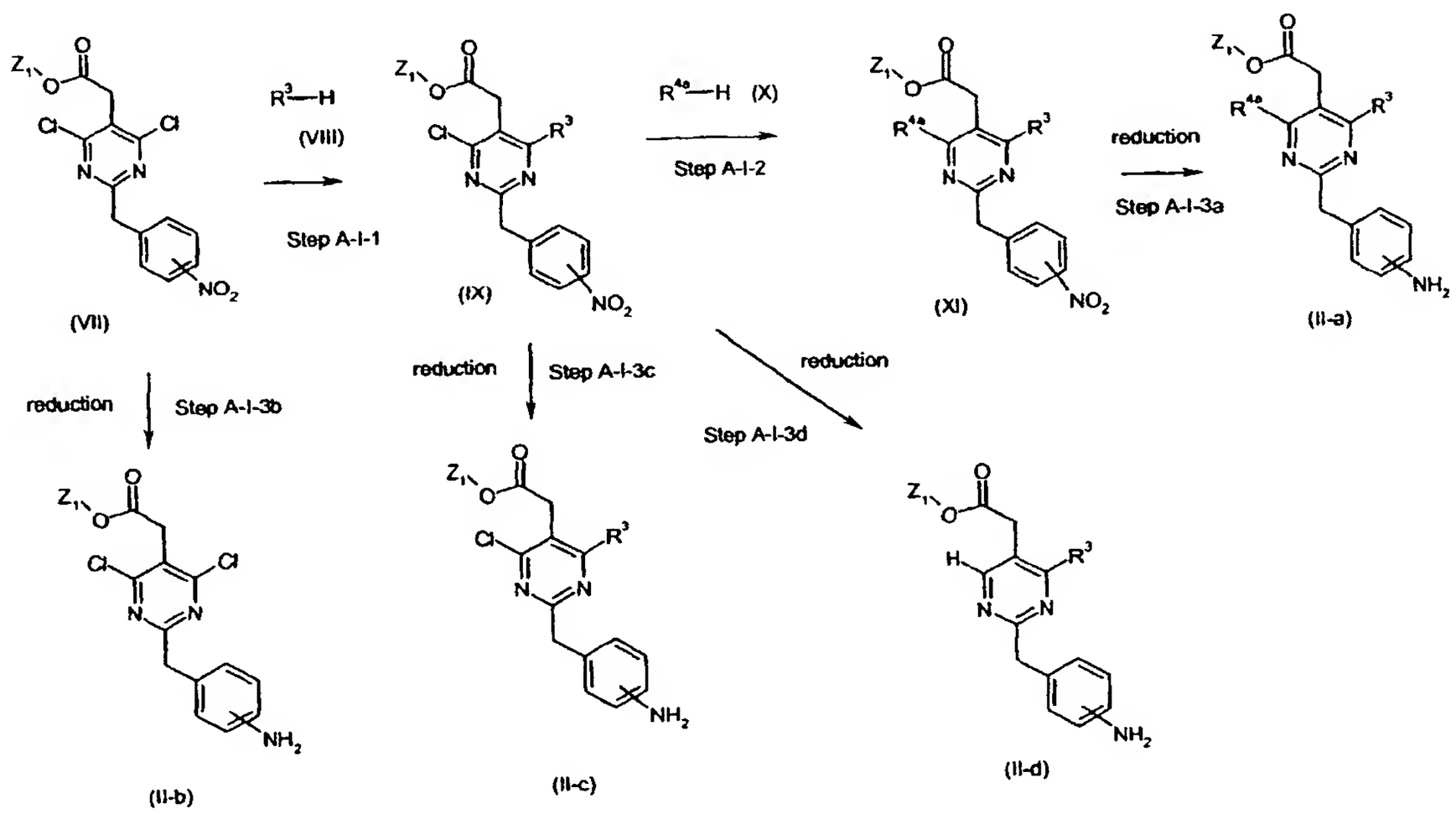
[0060] The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

[0061] Compounds of the formula (III), (IV) and (V) are commercially available or can be synthesized by conventional methods.

Preparation of starting compounds

Procedure A-I

[0062]



[0063] Compounds of the formula (II-a) (wherein R^3 and Z_1 are the same as defined above and R^{4a} is C_{1-6} alkoxy or di(C_{1-6} alkyl)amino) can be , for instance, prepared by the following procedures.

[0064] In Step A-I-1, compounds of the formula (VII) (wherein Z_1 is the same as defined above) is reacted with compounds of the formula (VIII) (wherein R^3 is the same as defined above) to give compounds of the formula (IX) (wherein R^3 and Z_1 are the same as defined above).

[0065] The reaction may be carried out without solvent or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides

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such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

[0066] The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 60 hours and preferably 1 to 48 hours.

[0067] The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine, N,N-diisopropylethylamine, dimethylaniline, diethylaniline, and others.

[0068] Compounds of the formula (XI) (wherein R^3 and Z_1 are the same as defined above and R^{4a} is C_{1-6} alkoxy or di(C_{1-6} alkyl)amino) can be prepared by the reaction of compounds of the formula (IX) (wherein R^3 an Z_1 are the same as defined above) with compounds of the formula (X) (wherein R^{4a} is C_{1-6} alkoxy or di(C_{1-6} alkyl)amino) in a similar manner described in Step A-I-1 for the preparation of compounds of the formula (IX), as shown in Step A-I-2.

[0069] In Step A-I-3a, compounds of the formula (II-a) (wherein R^3, R^{4a} and Z_1 are the same as defined above) can be prepared by reducing the nitro group of compounds of the formula (XI) (wherein R^3, R^{4a} and Z_1 are the same as defined above) using an agent including, for instance, metals such as zinc and iron in the presence of acid including, for instance, hydrochloric acid and acetic acid and stannous chloride, or by hydrogenation using a catalyst including, for instance, palladium on carbon and platinum on carbon.

[0070] The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane, aromatic hydrocarbons such as benzene, toluene and xylene, alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others.

[0071] The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 24 hours and preferably 1 to 12 hours.

[0072] In Step A-I-3b, compounds of the formula (II-b) (wherein Z_1 is the same as defined above) can be prepared by reducing the nitro group of compounds of the formula (VII) (wherein Z_1 is the same as defined above) in a similar manner described in Step A-I-3a for the preparation of compounds of the formula (II-a).

[0073] In Step A-I-3c, compounds of the formula (II-c) (wherein R^3 and Z_1 are the same as defined above) can be prepared by reducing the nitro group of compounds of the formula (IX) (wherein R^3 and Z_1 are the same as defined above) in a similar manner described in Step A-I-3a for the preparation of compounds of the formula (II-a).

[0074] In Step A-I-3d, compounds of the formula (II-d) (wherein R^3 and Z_1 are the same as defined above) can be prepared by reducing the nitro group and the chloro group of compounds of the formula (IX) (wherein R^3 and Z_1 are the same as defined above) by hydrogenation using a catalyst including, for instance, palladium on carbon and platinum on carbon in the presence of a base such as potassium acetate.

[0075] The reaction can be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane, tetrahydrofuran (THF) and 1,2-dimethoxyethane, aromatic hydrocarbons such as benzene, toluene and xylene, alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others.

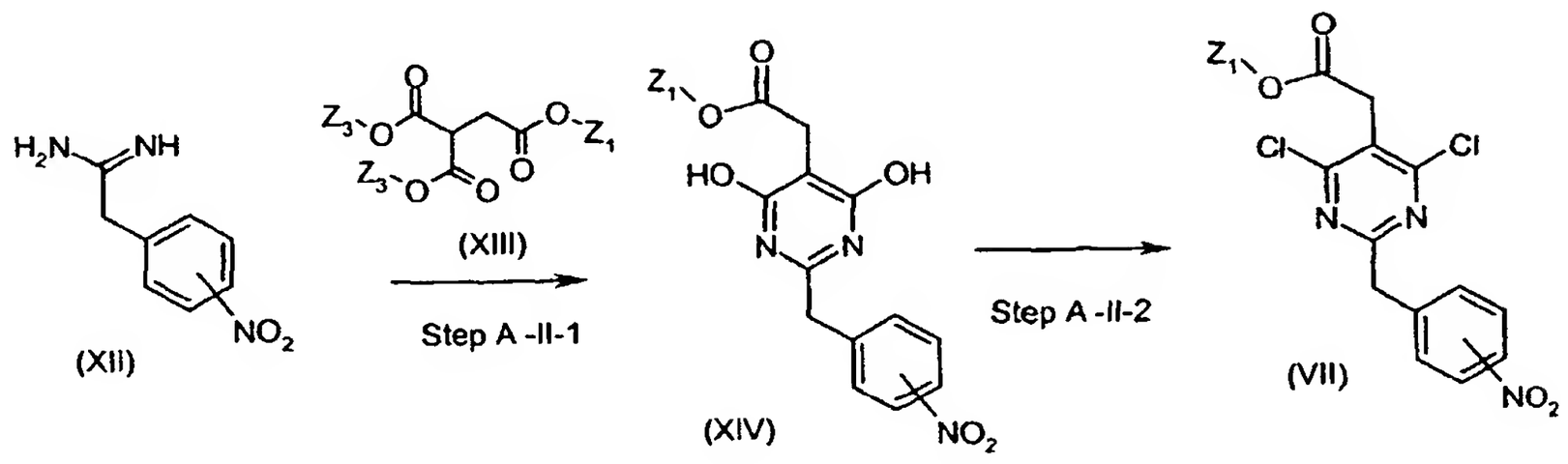
[0076] The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 24 hours and preferably 1 to 12 hours.

[0077] Compounds of the formula (VIII) and (X) are commercially available or can be synthesized by conventional methods.

Preparation of compounds of the formula (VII)

Procedure A-II

[0078]



[0079] Compounds of the formula (VII) (wherein Z_1 is the same as defined above) can be , for instance, prepared by the following procedures.

[0080] In Step A-II-1, compounds of the formula (XII) is reacted with compounds of the formula (XIII) (wherein Z_1 is the same as defined above and Z_3 is C_{1-6} alkyl) to give compounds of the formula (XIV) (wherein Z_1 is the same as defined above).

[0081] The reaction may be carried out in a solvent including, for instance, alcohols such as methanol, ethanol, 1-propanol, isopropanol and *tert*-butanol.

[0082] The reaction temperature can be optionally set depending on compoundss to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 30 hours and preferably 1 to 24 hours.

[0083] The reaction can be advantageously carried out in the presence of a base such as sodium methoxide.

[0084] In Step A-II-2, compounds of the formula (VII) (wherein Z_1 is the same as defined above) can be can be prepared for instance, by the reaction of compounds of the formula (XIV) (wherein Z_1 is the same as defined above) with an appropriate halogenating reagent including, for instance, $POCl_3$, PCl_5, and the like;

[0085] The reaction may be carried out without solvent or in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane, aromatic hydrocarbons such as benzene, toluene, and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

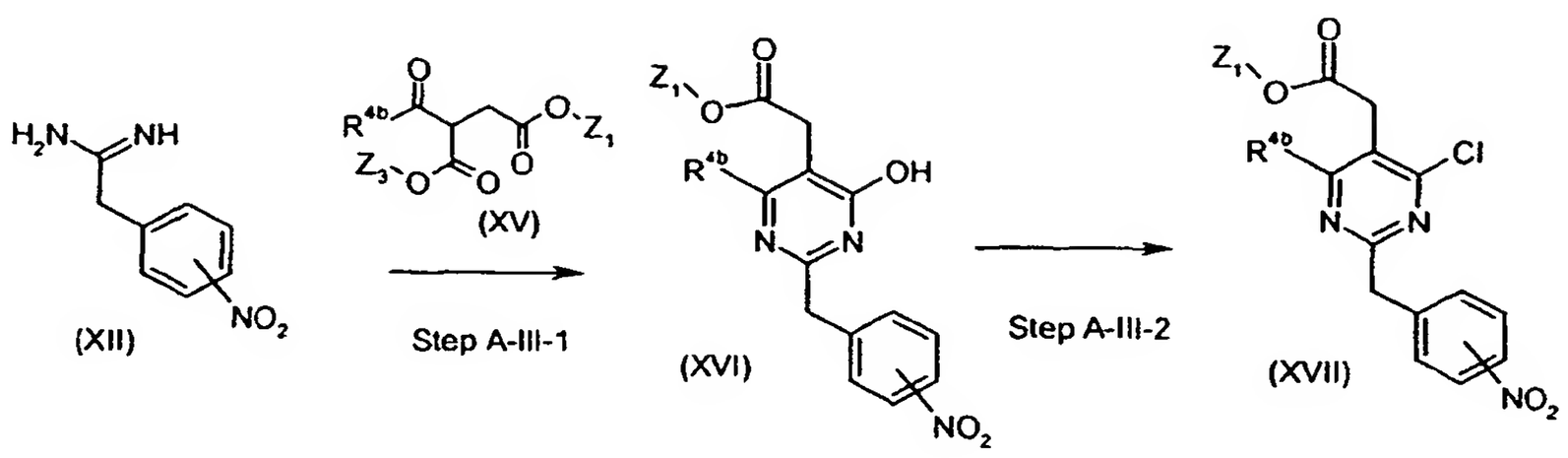
[0086] The reaction can be advantageously conducted in the presence of a base, including, for instance, pyridine, triethylamine and N,N-diisopropylethylamine, N. N-dimethylaniline, diethylaniline, and others.

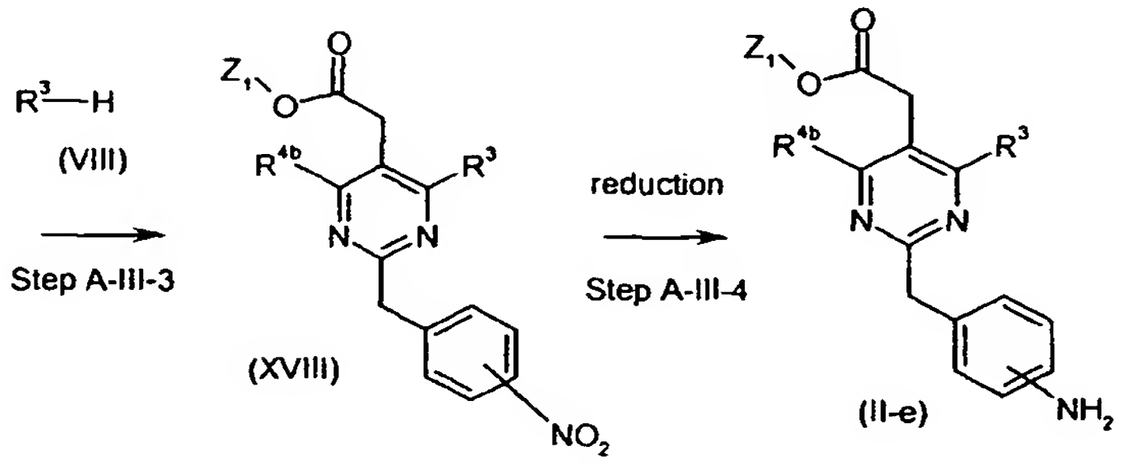
[0087] The reaction temperature is usually, but not limited to, about 40°C to 200°C and preferably about 20°C to 180°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hour to 12 hours.

[0088] Compounds of the formula (XII) and (XIII) are commercially available or can be synthesized by conventional methods.

Procedure A-III

[0089]





[0090] Compounds of the formula (II-e) (wherein R^3 and Z_1 are the same as defined above and R^{4b} is C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen) can be , for instance, prepared by the following procedures.

[0091] In Step A-III-1, compounds of the formula (XVI) (wherein R^{4b} and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (XII) and compounds of the formula (XV) (wherein R^{4b}, Z_1 and Z_3 are the same as defined above) in a similar manner described in Step A-II-1 for the preparation of compounds of the formula (XIV).

[0092] In Step A-III-2, compounds of the formula (XVII) (wherein R^{4b} and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (XVI) (wherein R^{4b} and Z_1 are the same as defined above) with an appropriate halogenating reagent in a similar manner described in Step A-II-2 for the preparation of compounds of the formula (VII).

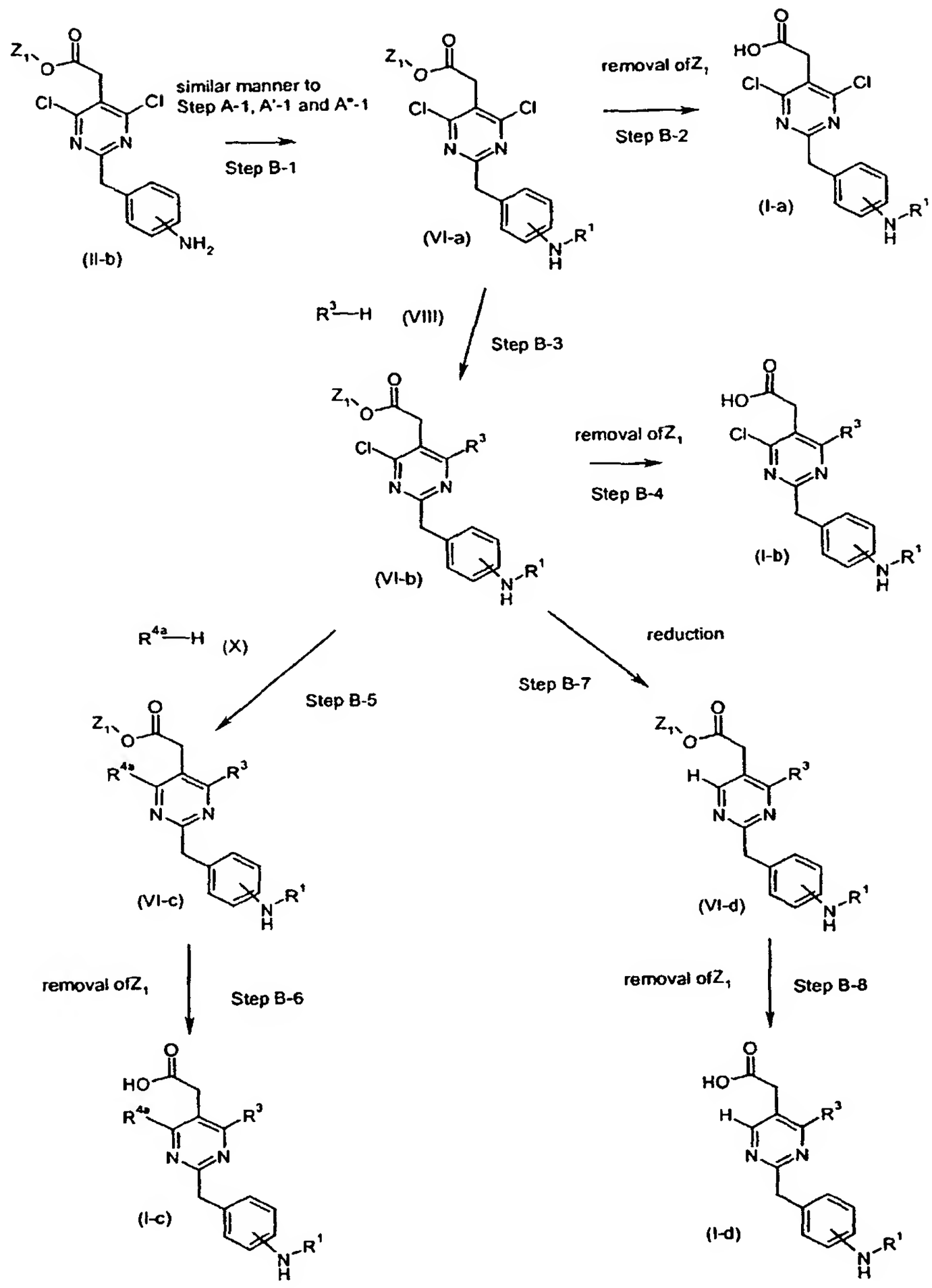
[0093] In Step A-III-3, compounds of the formula (XVIII) (wherein R^3, R^{4a} and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (XVII) (wherein R^{4b} an Z_1 are the same as defined above) with compounds of the formula (VIII) (wherein R^3 is the same as defined above) in a similar manner described in Step A-I-1 for the preparation of compounds of the formula (IX).

[0094] In Step A-III-4, compounds of the formula (II-e) (wherein R^3, R^{4a} and Z_1 are the same as defined above) can be prepared by reducing the nitro group of compounds of the formula (XVIII) (wherein R^3, R^{4a} and Z_1 are the same as defined above) in a similar manner described in Step A-I-3a for the preparation of compounds of the formula (II-a).

[0095] Compounds of the formula (XV) is commercially available or can be synthesized by conventional methods.

[Method B]

[0096]



[0097] Compounds of the formula (I-a) (wherein R^1 is the same as defined above), the formula (I-b) (wherein R^1 and R^3 are the same as defined above), the formula (I-c) (wherein R^1, R^3 and R^{4a} are the same as defined above) and the formula (I-d) (wherein R^1 and R^3 are the same as defined above) can also be prepared by the following procedures.

[0098] In Step B-1, compounds of the formula (VI-a) (wherein R^1 and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (II-b) (wherein Z_1 is the same as defined above) in a similar manner described in Step A-1, A'-1 and A"-1 for the preparation of compounds of the formula (VI).

[0099] In Step B-2, compounds of the formula (I-a) (wherein R^1 is the same as defined above) can be prepared by the removal of protective group Z_1 of compounds of the formula (VI-a) (wherein R' and Z_1 are the same as defined above) in a similar manner of Step A-2 for the preparation of compounds of the formula (I).

[0100] In Step B-3, compounds of the formula (IV-b) (wherein R^1, R^3 and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (VI-a) (wherein R^1 and Z_1 are the same as defined above) with compounds of the formula (VIII) (wherein R^3 is the same as defined above) in a similar manner described in Step A-I-1 for the preparation of compounds of the formula (IX).

[0101] In Step B-4, compounds of the formula (I-b) (wherein R^1 and R^3 are the same as defined above) can be prepared by the removal of protective group Z_1 of compounds of the formula (VI-b) (wherein R^1, R^3 and Z_1 are the same as defined above) in a similar manner of Step A-2 for the preparation of compounds of the formula (I).

[0102] In Step B-5, compounds of the formula (VI-c) (wherein R^1, R^3, R^{4a} and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (VI-b) (wherein R^1, R^3 and Z_1 are the same as defined above) with compounds of the formula (X) (wherein R^{4a} is the same as defined above) in a similar manner described in Step A-I-2 for the preparation of compounds of the formula (XI).

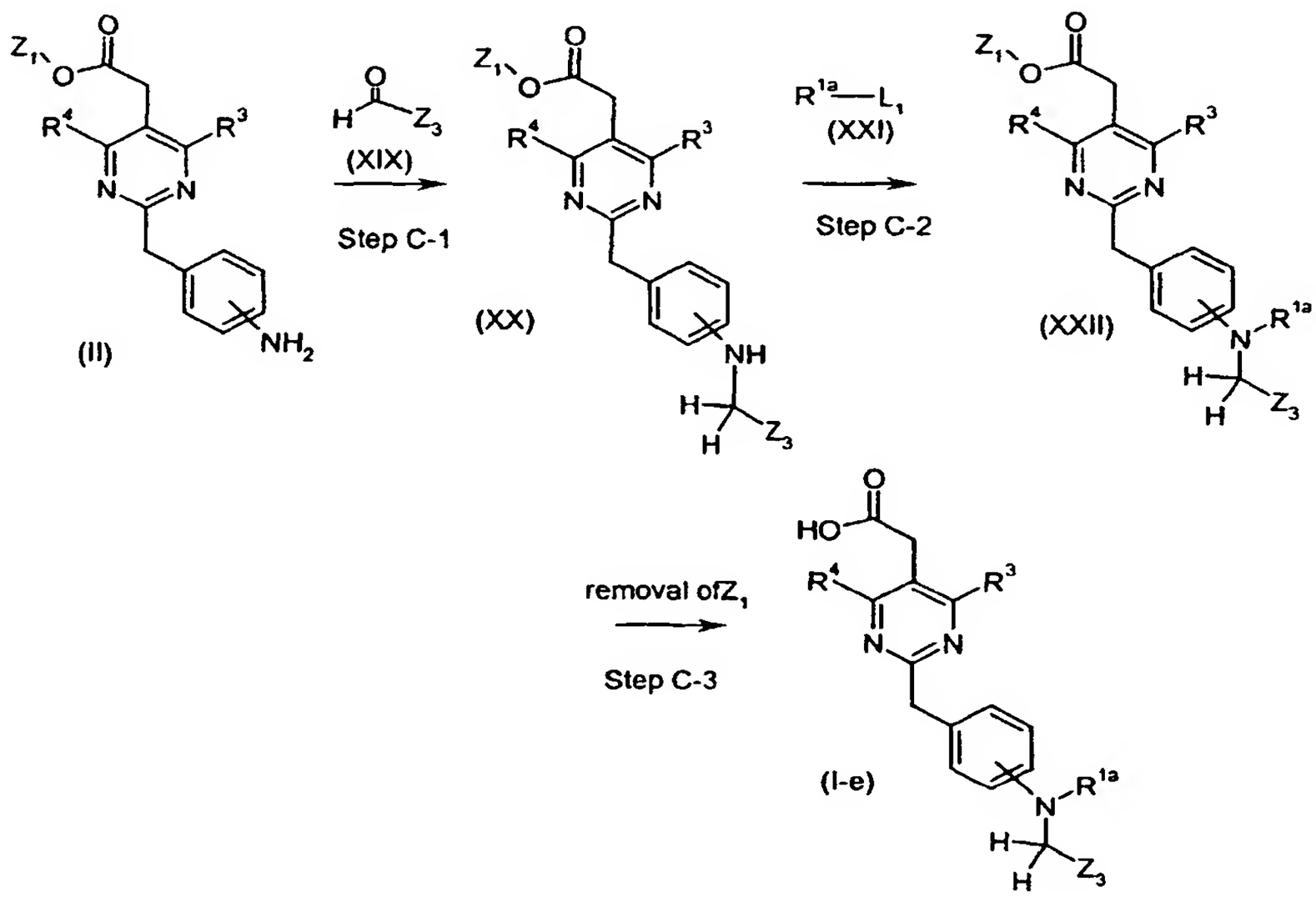
[0103] In Step B-6, compounds of the formula (I-c) (wherein R^1, R^3 and R^{4a} are the same as defined above) can be prepared by the removal of protective group Z_1 of compounds of the formula (VI-b) (wherein R^1, R^3, R^{4a} and Z_1 are the same as defined above) in a similar manner of Step A-2 for the preparation of compounds of the formula (I).

[0104] In Step B-7, compounds of the formula (VI-d) (wherein R^1, R^3 and Z_1 are the same as defined above) can be prepared by the reaction of compounds of the formula (VI-b) (wherein R^1, R^3 and Z_1 are the same as defined above) in a similar manner described in Step Step A-I-3d for the preparation of compounds of the formula (II-d).

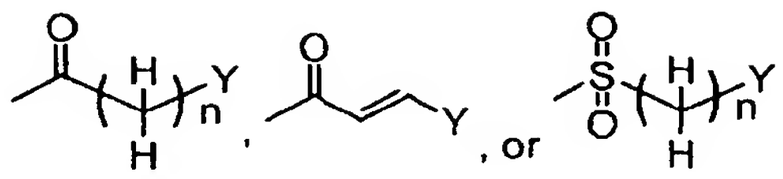
[0105] In Step B-8, compounds of the formula (I-d) (wherein R^1 and R^3 are the same as defined above) can be prepared by the removal of protective group Z_1 of compounds of the formula (VI-d) (wherein R^1, R^3 and Z_1 are the same as defined above) in a similar manner of Step A-2 for the preparation of compounds of the formula (I).

[Method C]

[0106]



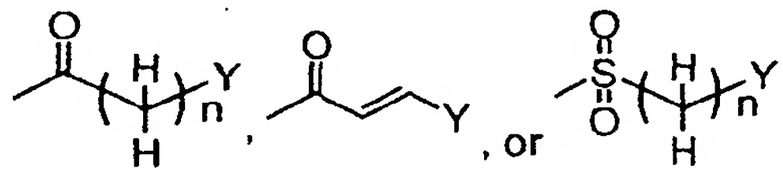
[0107] Compounds of the formula (I-e) (wherein R^3 and R^4 are the same as defined above, R^{1a} represents



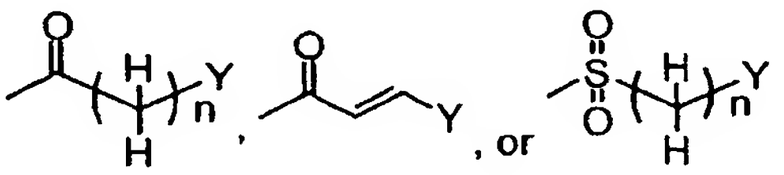
in which n and Y are the same as defined above and Z_3 represents hydrogen or C_{1-5} alkyl) can also be prepared by the following procedures.

[0108] In Step C-1, compounds of the formula (XX) (wherein R^3, R^4, Z_1 and Z_3 are the same as defined above) can be prepared by the reaction of compounds of the formula (II) (wherein R^3, R^4 and Z_1 are the same as defined above) with compounds of the formula (XIV) (wherein Z_3 is the same as defined above) in a similar manner described in Step A'-1 for the preparation of compounds of the formula (VI).

[0109] In Step C-2, compounds of the formula (XXII) (wherein R^3, R^4, Z_1 and Z_3 are the same as defined above and R^{1a} represents



in which n and Y are the same as defined above) can be prepared by the reaction of compounds of the formula (XX) (wherein R^3, R^4, Z_1 and Z_3 are the same as defined above) with compounds of the formula (XXI) (wherein R^{1a} represents



in which n and Y are the same as defined above and L_1 is the same as defined above) in a similar manner described in Step A-1 for the preparation of compounds of the formula (VI).

[0110] In Step C-3, compounds of the formula (I-e) (wherein R^{1a}, R^3, R^4 and Z_3 are the same as defined above) can be prepared by the removal of protective group Z_1 of compounds of the formula (XXII) (wherein R^{1a}, R^3, R^4, Z_1 and Z_3 are the same as defined above) in the same manner of Step A-2 for the preparation of compounds of the formula (I).

[0111] Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

[0112] Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

[0113] Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

[0114] The compound of the present invention or salts thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

[0115] The compound of the present invention may be administered in oral forms, such as, without limitation, normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those

of ordinary skilled in the art.

[0116] The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

[0117] The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation, carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

[0118] Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

[0119] For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

[0120] In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

[0121] Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

[0122] The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

[0123] The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

[0124] Typical oral dosages of the compound of the present invention, when used for the indicated effects, will range from about 1 mg /kg/day to about 10 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

EXAMPLES

[0125] The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

[0126] In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

[0127] Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). Melting points are uncorrected. Liquid Chromatography - Mass spectroscopy (LC-MS) data were recorded on a Micromass Platform LC with Shimadzu Phenomenex ODS column(4.6 mmϕ X 30 mm) flushing a mixture of acetonitrile-water (9: 1 to 1:9) at 1 ml/min of the flow rate. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254).

Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Great Britain, Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Germany, Kanto Chemical Co., Ltd.

[0128] ^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H). Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doblet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

[0129] All starting materials are commercially available or can be prepared using methods cited in the literature.

[0130] The effect of the present compounds was examined by the following assays and pharmacological tests.

EXAMPLE 1

[Preparation of human CRTH2-transfected L1.2 cell line]

[0131] Human CRTH2 cDNA was amplified from human eosinophil cDNA with gene specific primers containing restriction sites for cloning into pEAK vector (Edge Bio Systems). The human CRTH2 cDNA was cloned into the mammalian expression vector pEAK. This expression plasmid (40 μg) was transfected into L1.2 cells, at a cell density of $1x10^7$ cells/500 μl, by using electroporation apparatus (Gene Pulser II, BioRad) at 250V/1,000 μF. One day after the transfection, puromycin (1 μg/ml, Sigma) was added into the cell culture plates. Two weeks after the transfection, grown cells were picked up for further growth.

[Measurement of Ca^{2+} mobilization in the human CRTH2-transfected L1.2 cell line] (Assay 1)

[0132] Ca^{2+} loading buffer was prepared by mixing 5 μl of Fluo-3AM (2 mM in DMSO, final 1 μM, Molecular Probes) and 10 μl of pluronic F-127 (Molecular Probes) and diluting the resulting mixture in 10 ml of Ca^{2+} assay buffer (20 mM HEPES pH 7.6, 0.1% BSA, 1 mM probenecid, Hanks' solution). The CRTH2 transfected cells which were prepared in Example 1 were washed with PBS, resuspended in Ca^{2+} loading buffer at 1 x 10^7 cells/ml, and incubated for 60 min at room temperature. After incubation, cells were washed and resuspended in Ca^{2+} assay buffer, then dispensed into transparent-bottom 96-well plates (#3631, Costar) at 2 x 10^5 cells/well. Cells were incubated with various concentrations of test compound for 5 minutes at room temperature. The emitted 480 nm fluorescence was measured on FDSS6000, a Ca^{2+} - measurement apparatus (Hamamatsu Photonics, Hamamatsu, Japan). The transfectant showed PGD_2-induced Ca^{2+} mobilization in a concentration-dependent manner.

[human CRTH2 receptor binding assay] (Assay 2)

[0133] CRTH2 transfectants were washed once with PBS and resuspended in binding buffer (50 mM Tris-HCl, pH7.4, 40 mM $MgCl_2$, 0.1% BSA, 0.1% NaN_3). 100 μl of cell suspension (2 x 10^5 cells), [^{3}H]-labeled PGD_2, and various concentrations of test compound were then mixed in a 96-well U-bottom polypropylene plate and incubated for 60 min at room temperature to allow binding to occur. After incubation, the cell suspension was transferred to a filtration plate (#MAFB, Millipore) and washed 3 times with binding buffer. Scintillant was added to the filtration plate, and radioactivity remaining on the filter was measured by TopCount (Packard), a scintillation counter. Non-specific binding was determined by incubating the cell suspension and [^{3}H]-labeled PGD_2 in the presence of 1 μM of unlabeled PGD_2. Puromycin-resistant L1.2 transfectants bound to [^{3}H]-labeled PGD_2 with high affinity (K_D = 6.3 nM).

[Migration assay of human eosinophils] (Assay 3)

[0134] Human polymorphonuclear cells were isolated from heparinized venous blood of healthy donors by laying the blood on Mono-Poly Resolving Medium (ICN Biomedicals, Co.Ltd) and centrifuging it at 400 x g for 30 min. at room temperature. After centrifugation, eosinophils were purified from the lower layer of polymorphonuclear cells by CD16-negative selection using anti-CD16-conjugated magnetic beads (Miltenyi Biotech GmbH).

[0135] Human eosinophils were washed with PBS and resuspended in chemotaxis buffer (20 mM HEPES pH 7.6, 0.1% BSA, Hanks' solution) at 6 x 10^6 cells/ml. Fifty μl of the cell suspension (3 x 10^5 cells/well) was then dispensed into the upper chamber and 30 μl of ligand solution (PGD_2, 1 nM, final concentration) was added to the lower chamber of a 96-well chemotaxis chamber (Diameter = 5 μm, #106-5, Neuro Probe). Cells were preincubated with various concentrations of test compound at 37 °C for 10 minutes. Chemotaxis is then allowed to occur in a humidified incubator at 37 °C, 5% CO_2 for 2 hours. The number of cells migrating into the lower chamber was counted by FACScan (Becton-

Dickinson).

[Migration assay of human CD4+ T cells] (Assay 4)

[0136] Human mononuclear cells were isolated from heparinized venous blood of healthy donors by laying the blood on Mono-Poly Resolving Medium (ICN Biomedicals, Co.Ltd) and centrifuging it at 400 x g for 30 min. at toom temperature. After centrifugation, $CD4^+$ T lymphocytes were purified from mononuclear cells by using $CD4^+$ T cell isolation kit (Miltenyi Biotec GmbH).

[0137] Human $CD4^+$ T lymphocytes were washed with PBS and resuspended in chemotaxis buffer (20 mM HEPES pH 7.6, 0.1% BSA, Hanks' solution) at 6 x 10^6 cells/ml. Fifty µl of the cell suspension (3 x 10^5 cells/well) was then dispensed into the upper chamber and 30 µl of ligand solution (PGD_2, 10 nM, final concentration) was added to the lower chamber of a 96-well chemotaxis chamber (Diameter = 3 mm, #106-3, Neuro Probe). Cells were preincubated with various concentrations of test compound at 37 °C for 10 minutes. Chemotaxis is then allowed to occur in a humidified incubator at 37 °C, 5% CO_2 for 4 hours. The number of cells migrating into the lower chamber was counted by FACScan (Becton-Dickinson).

[0138] Assay results in Assay 1 are shown in Examples and tables of the Examples below. The data corresponds to the compounds as yielded by solid phase synthesis and thus to levels of purity of about 40 to 90%. For practical reasons, the compounds are grouped in four classes of activity as follows:

$$IC_{50} = A\ (< \text{or} =)\ nM < B\ (< \text{or} =)\ 0.5\ nM < C\ (< \text{or} =)\ 1\ nM < D$$

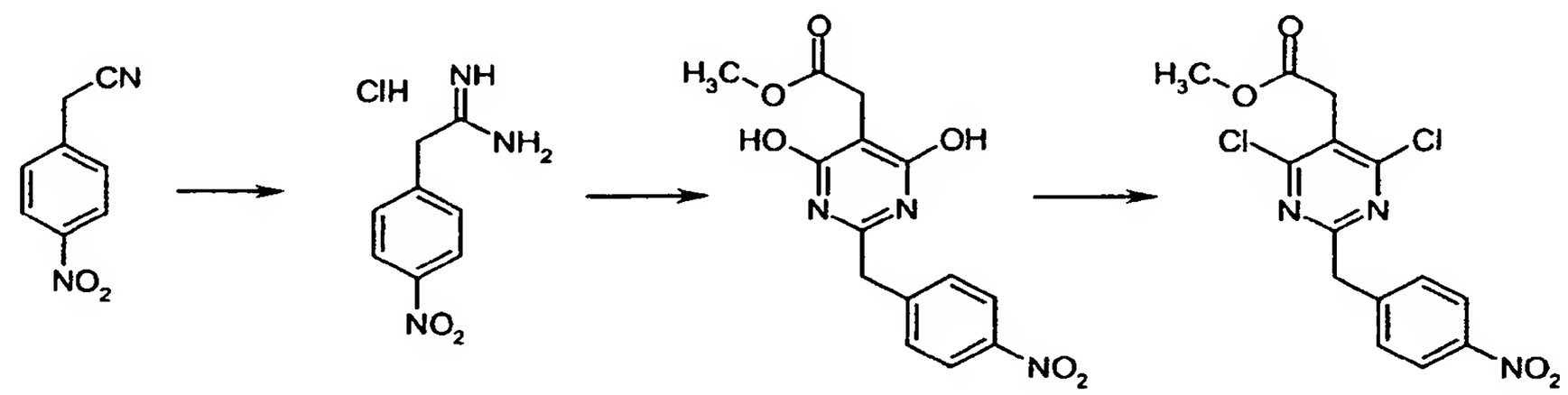
[0139] The compounds of the present invention also show excellent selectivity, and potent activity in Assays 2, 3 and 4 described above.

z used in Melting point in the following section indicates decomposition. All inorganic acids and bases were aqueous solutions unless otherwise stated. Eluent concentrations are expressed as %vol./vol.

Preparation of compounds

Methyl [4,6-dichloro-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate

[0140]



4-Nitrophenyl acetonitrile (81.07 g, 500 mmol) was suspended in EtOH (300 mL) and dioxane (300 mL) was added. After all solids had dissolved, dry HCl gas was bubbled through the reaction mixture for 1h and then stirred at r.t. for 15 h. Et_2O was then added and the separated solids were collected by suction and rinsed with Et_2O. This intermediate was dissolved in NH_3 saturated EtOH and the solution thus obtained was stirred at r.t. for 14 h. Excess solvent was removed *in vacuo* to give 2-(4-nitrophenyl)ethanimidamide hydrochloride (73.65 g, 68% yield) as a white powder.

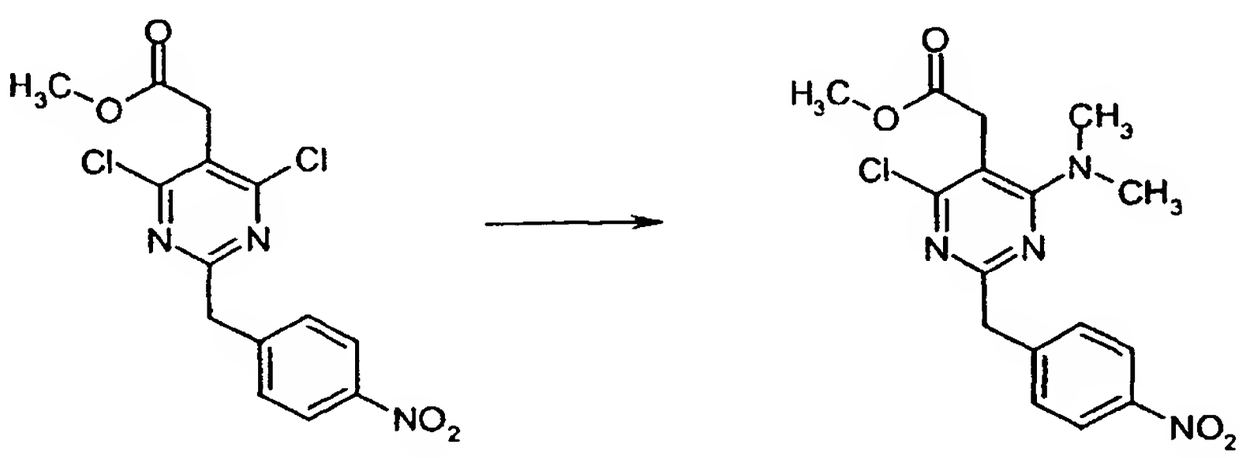
[0141] To a mixture of triethyl 1,1,2-ethanetricarboxylate (3.51 mL, 15.30 mmol) and 2-(4-nitrophenyl)ethanimidamide hydrochloride (46.95 g, 217.72 mmol) in anhydrous MeOH (300 mL) at r.t. was added NaOMe (3.8.82 g, 718.49 mmol) and the resulting suspension was refluxed for 16 h. After cooling to r.t., the reaction mixture was chilled to 0 °C, acidified with 6N HCl, and the separated solids collected by suction and rinsed with cold water. Drying under high vacuum at 45 °C for 6 h then gave methyl [4,6-dihydroxy-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (56.48 g, 81% yield) as a pale white powder.

[0142] To a suspension of methyl [4,6-dihydroxy-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (4.12 g, 12.89 mmol) in $POCl_3$ (24 mL) at r.t. and under Ar atmosphere was added N,N-dimethylaniline (8.17 mL, 64.44 mmol) and the resulting dark suspension was heated at reflux for 16 h. After cooling to r.t., excess $POCl_3$ was evaporated and the remaining

dark residue was dissolved in EtOAc. This organic layer was then washed sequentially with saturated $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product thus obtained was dissolved in CH_2Cl_2 and passed through a short plug of silica gel to afford pure methyl [4,6-dichloro-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (2.98 g, 65% yield) as an off-white powder.

Methyl [4-chloro-6-(dimethylamino)-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate

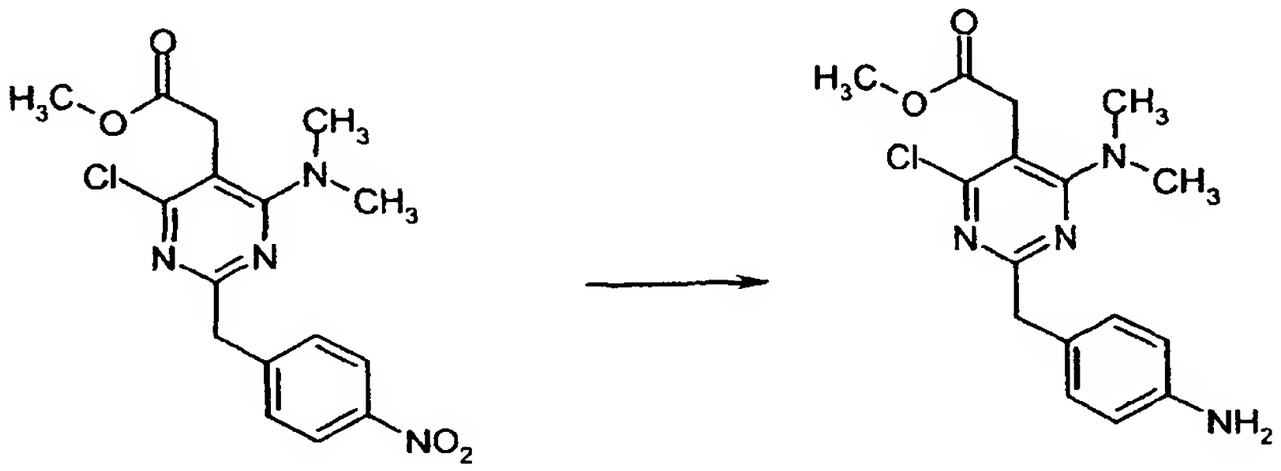
[0143]



[0144] To a solution of methyl [4,6-dichloro-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (0.5 g, 1.40 mmol) in anhydrous DMF (5 mL) at r.t. under Ar atmosphere was added *N,N*-diisopropylethylamine (0.0.54 mL, 3.09 mmol) and dimethylamine hydrochloride (0.126 g, 1.54 mmol). The resulting solution was stirred at 85 °C for 16 h at which time the reaction mixture was concentrated to dryness and the residue chromatographed over silica gel eluting with 50% EtOAc in *n*-hexane to give methyl [4-chloro-6-(dimethylamino)-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (0.505 g, 99% yield) as a brown oil.

Methyl [2-(4-aminobenzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetate

[0145]

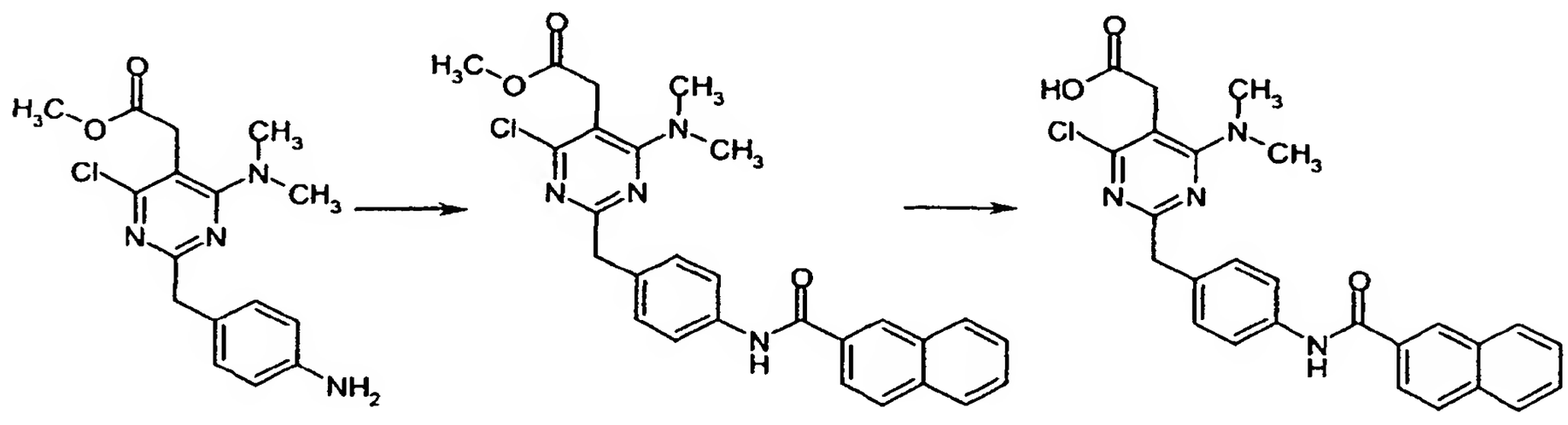


[0146] A solution of methyl [4-chloro-6-(dimethylamino)-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (1.00 g, 2.74 mmol) in anhydrous THF (20 mL) at r.t. was treated with 10% Pd/C (0.100 g) and the resulting black suspension was stirred under an atmosphere of hydrogen. After 13 h, the reaction mixture was filtered over Celite. Evaporation of the filtrate gave the crude product as a clear oil which was passed through a short column eluting with 40% EtOAc in n-hexane to give methyl [2-(4-aminobenzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetate (0.876 g, 95% yield) as a light orange oil which slowly solidified upon standing at r.t.

Example 1-1

{4-Chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid

[0147]



[0148] To a mixture of methyl [2-(4-aminobenzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetate (0.090 g, 0.30 mmol) and PyBOP (0.187 g, 0.36 mmol) in anhydrous DMF (1 mL) at r.t. was added 2-naphthoic acid (0.062 g, 0.36 mmol). The resulting reaction mixture was stirred at r.t. for 3 h at which time water was added and the resulting aqueous phase was extracted with EtOAc. The combined organic extracts was sequentially washed with 0.5N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give methyl {4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetate as a colorless oil.

[0149] The thus obtained methyl {4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetate was dissolved in THF (1 mL) and treated with 1N NaOH (0.5 mL). The resulting biphasic mixture was stirred at r.t. for 14 h at which time it was poured into water. The separated aqueous phase was washed with EtOAc and then acidified with 1N HCl and back extracted with EtOAc. The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product thus obtained was dissolved in a minimum volume of THF to which *n*-hexane was added. The separated precipitate was collected by suction, rinsed with *n*-hexane, and dried under vacuum to give {4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid (0.038 g, 40% yield) as a white powder.

[0150] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.05 (s, 6H), 3.67 (s, 2H), 3.93 (s, 2H), 7.32 (d, J=8 Hz, 2H), 7.59-7.68 (m, 2H), 7.75 (d, J=8 Hz, 2H), 8.00-8.10 (m, 4H), 8.57 (s, 1H), 10.40 (s, 1H), 12.77 (bs, 1H).

Molecular weight: 474.95

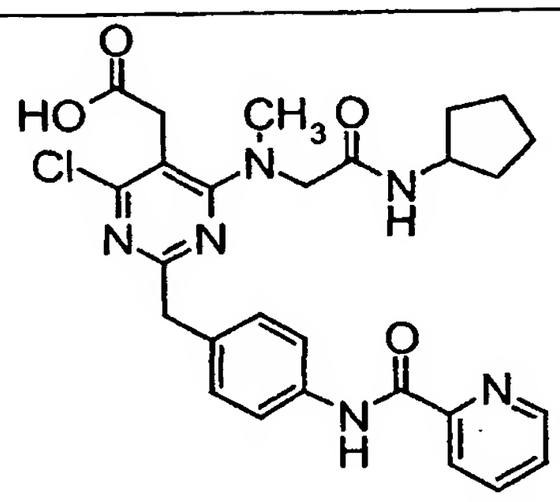
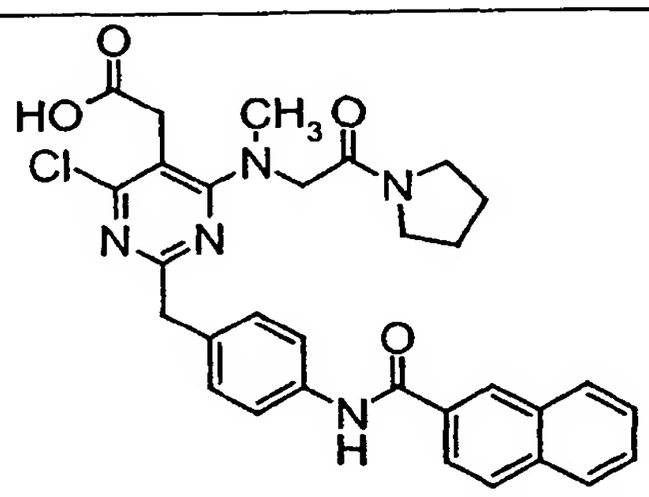
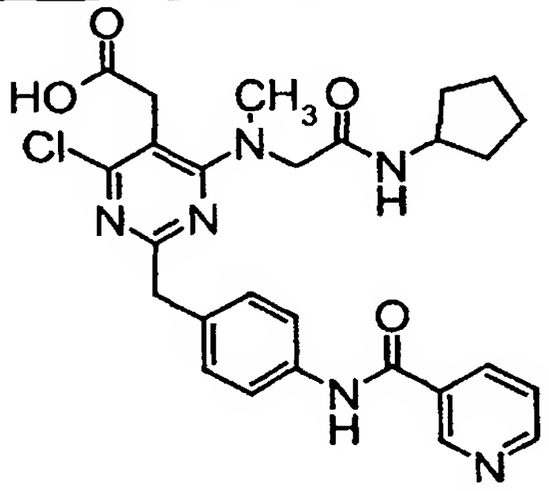
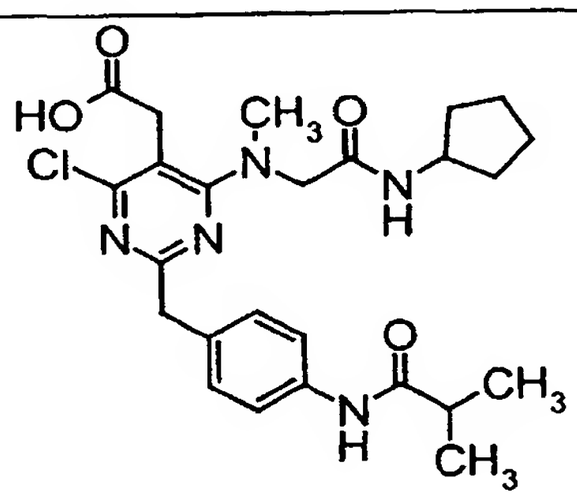
Mass spectrometry: 475

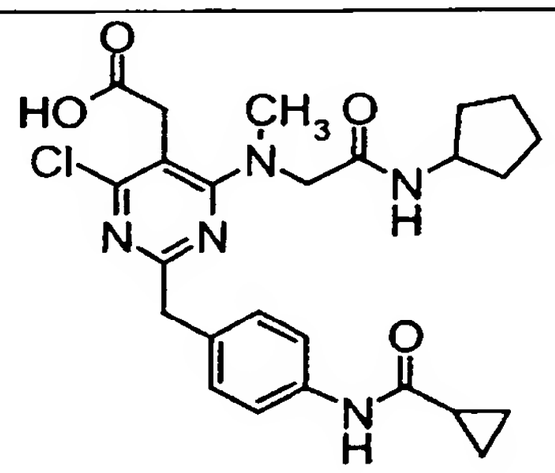
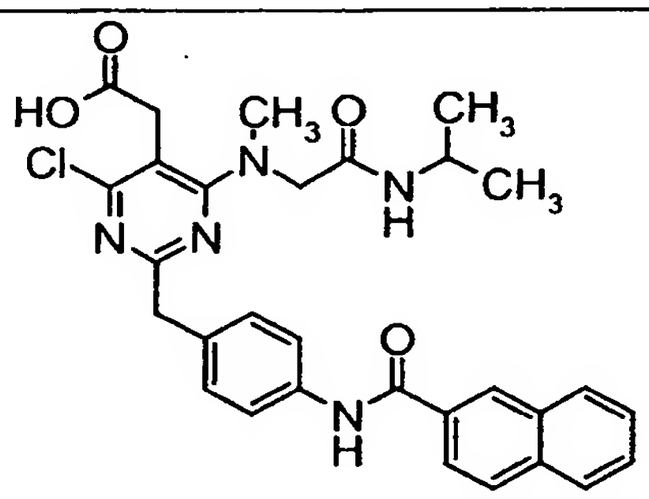
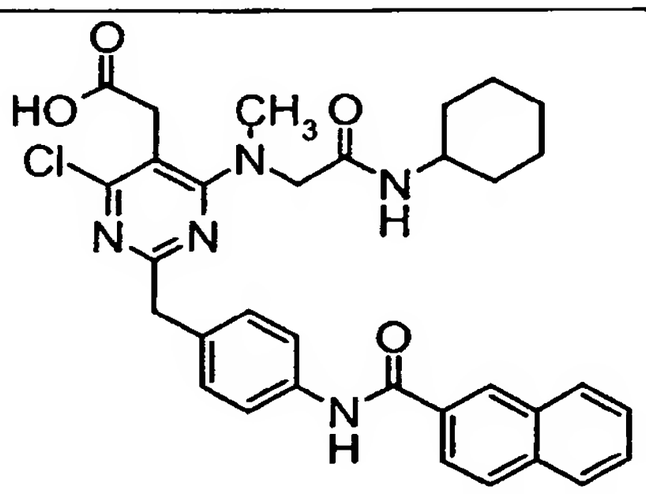
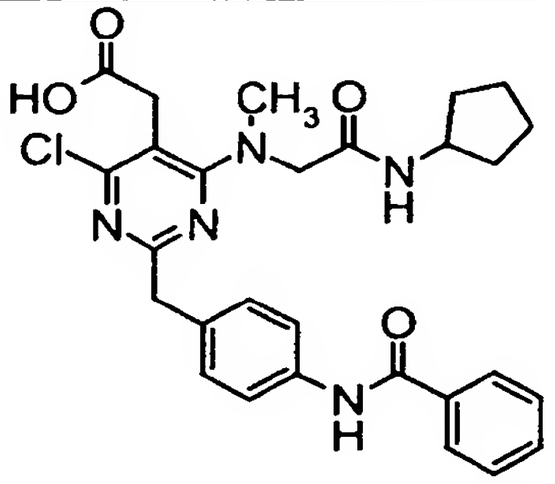
Melting point: 188 Z °C

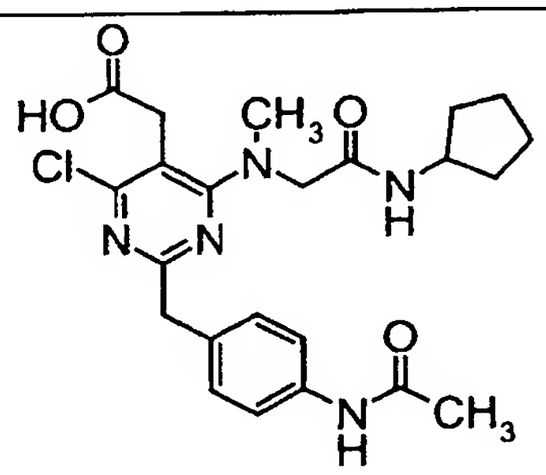
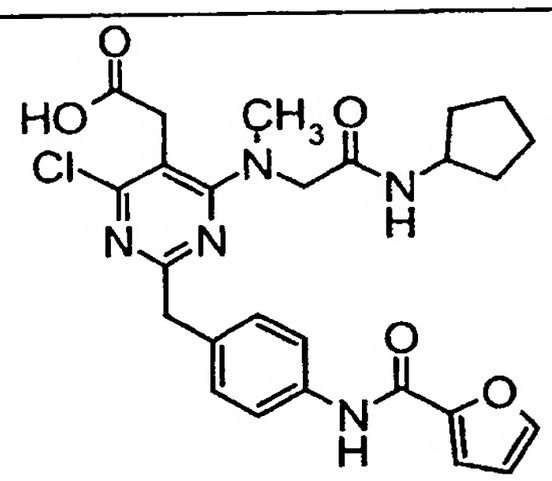
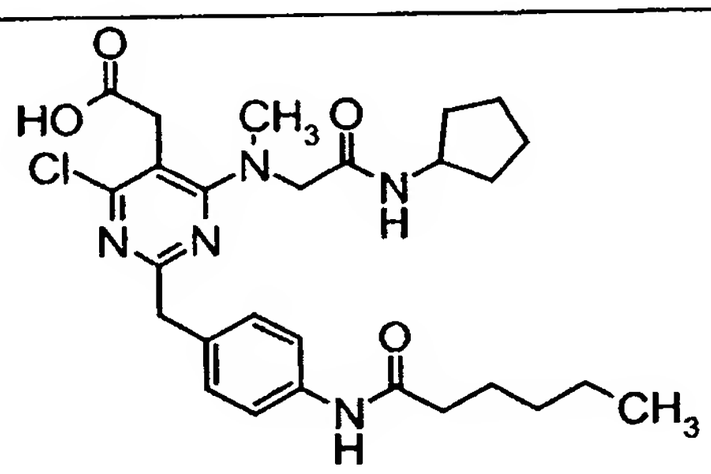
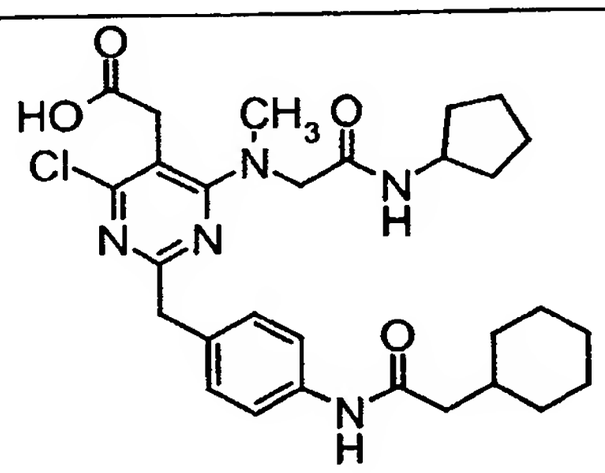
Activity class: A

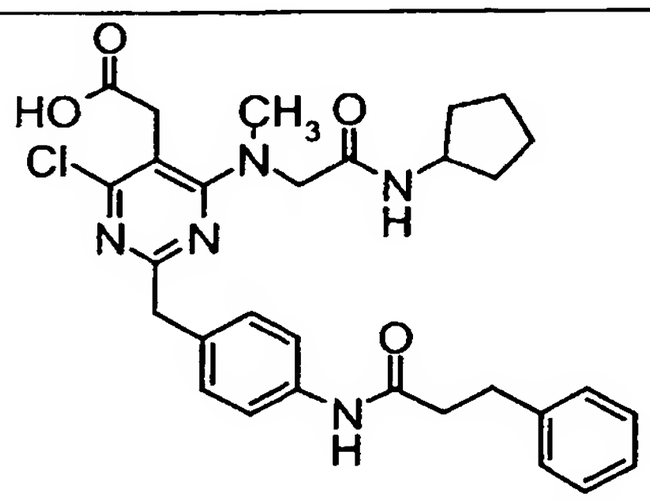
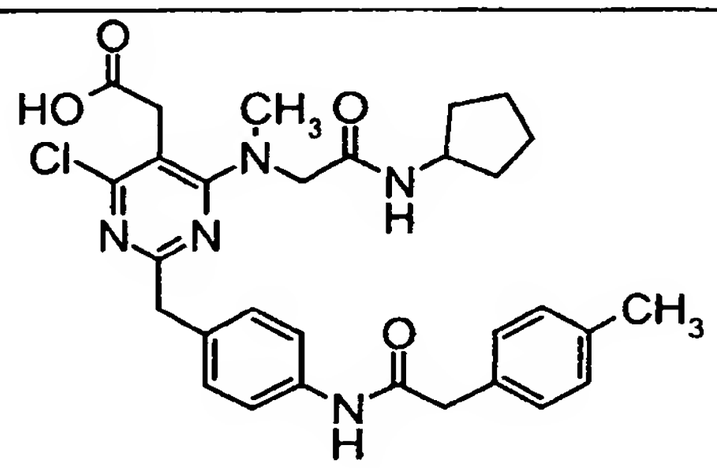
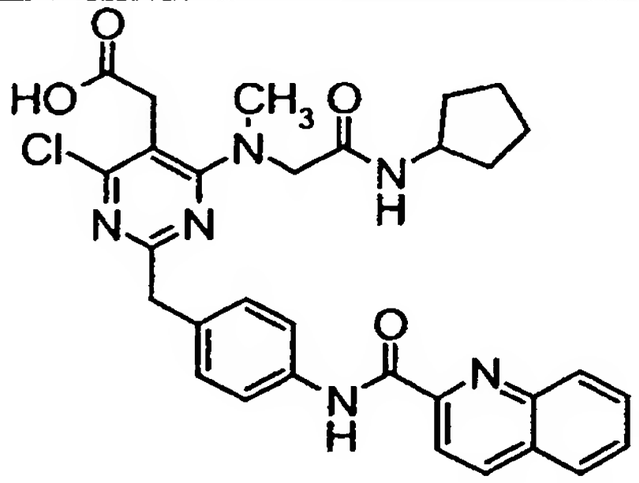
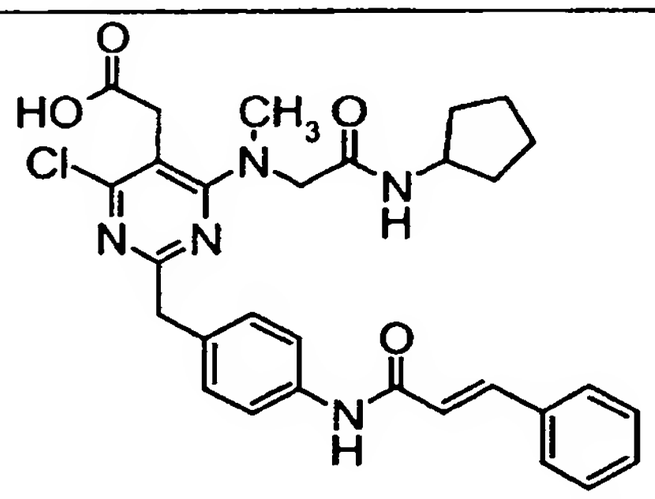
[0151] In a similar manner as described in Example 1-1, compounds in Example 1-2 to 1-62 as shown in Table 1 were synthesized.

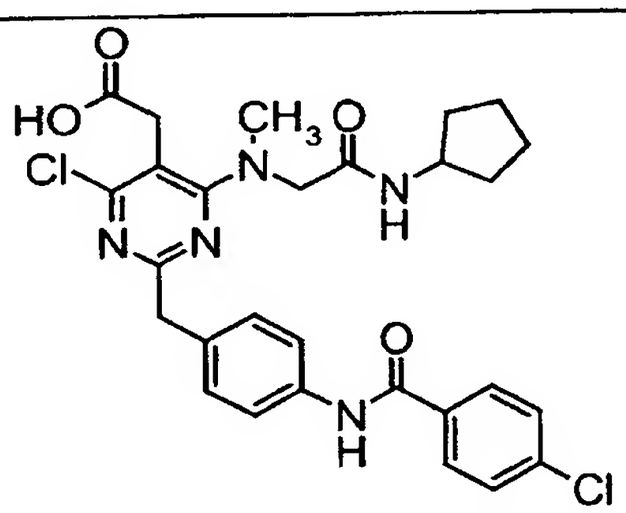
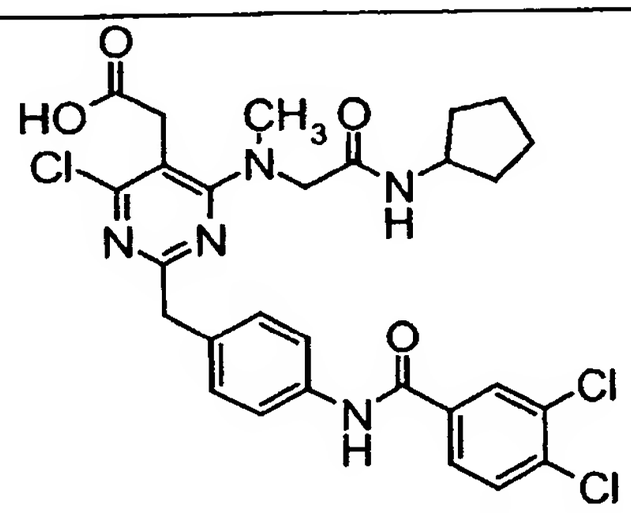
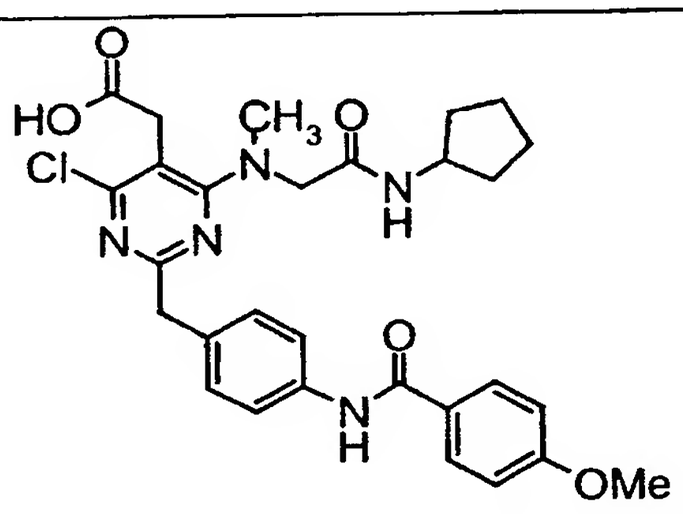
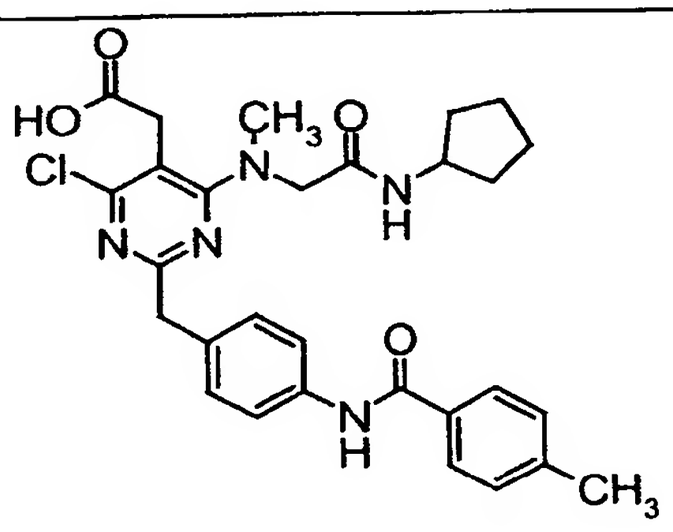
Table 1

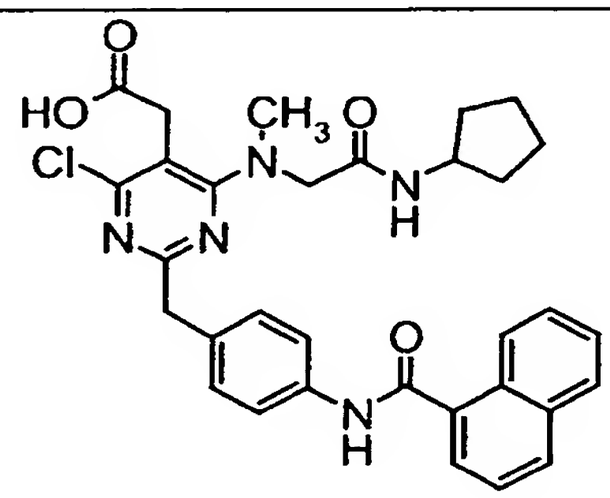
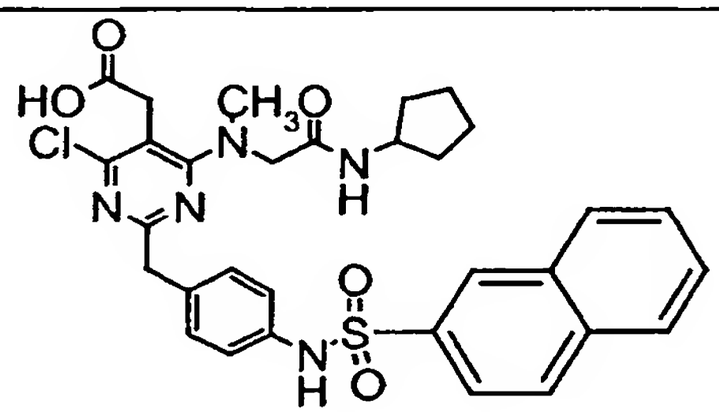
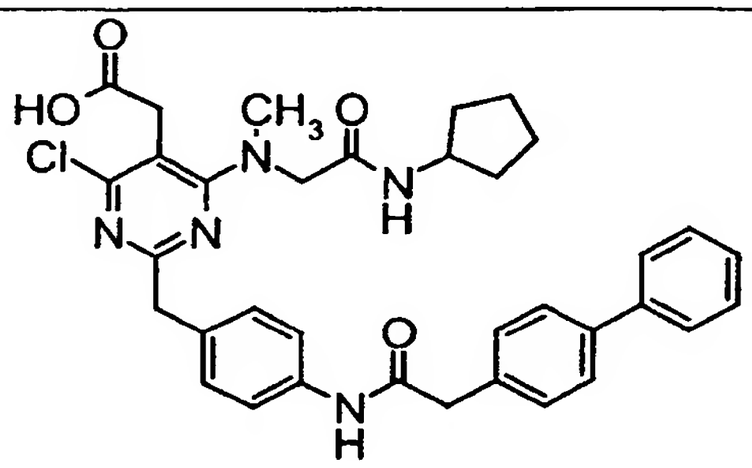
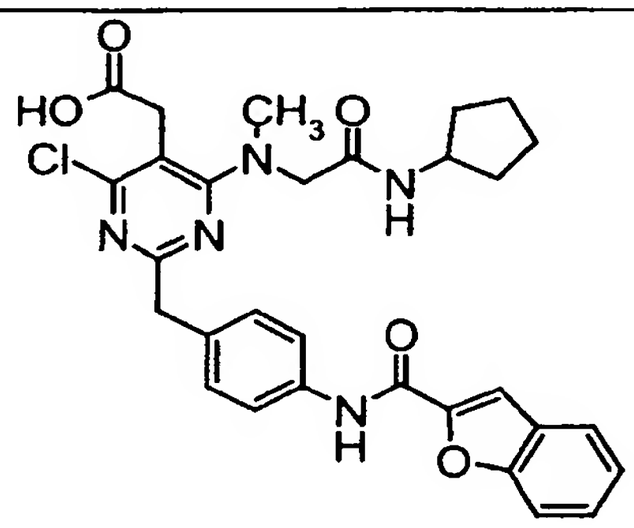
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-2		537,02	536	537	>135 Z	D
1-3		572,07	571	572	177 Z	A
1-4		537,02	536	537	>174 Z	D
1-5		502,02	501	502	>142 Z	D

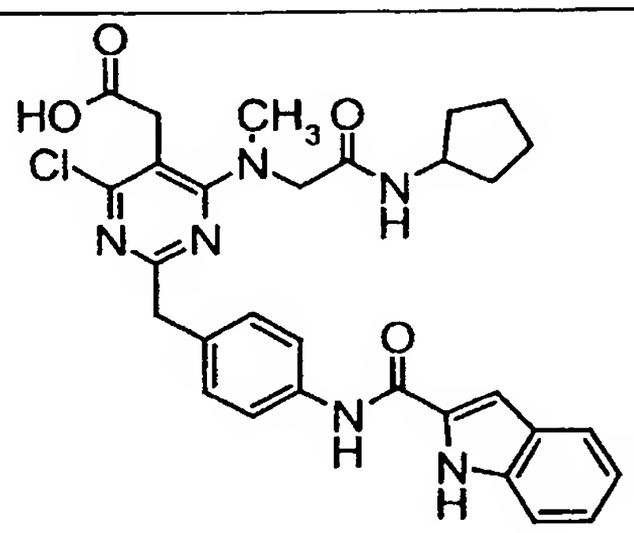
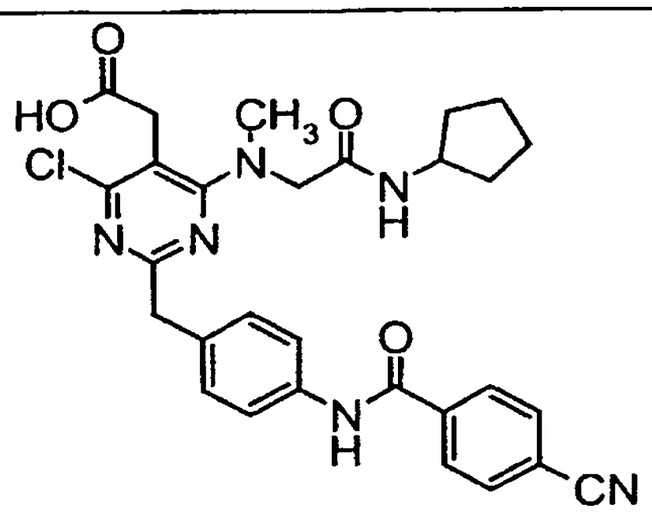
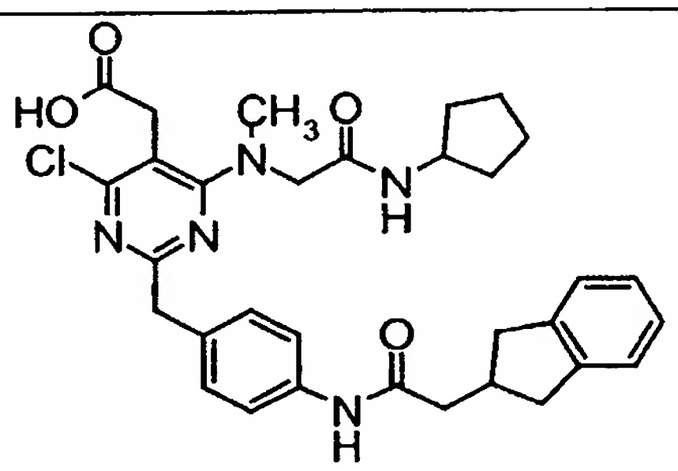
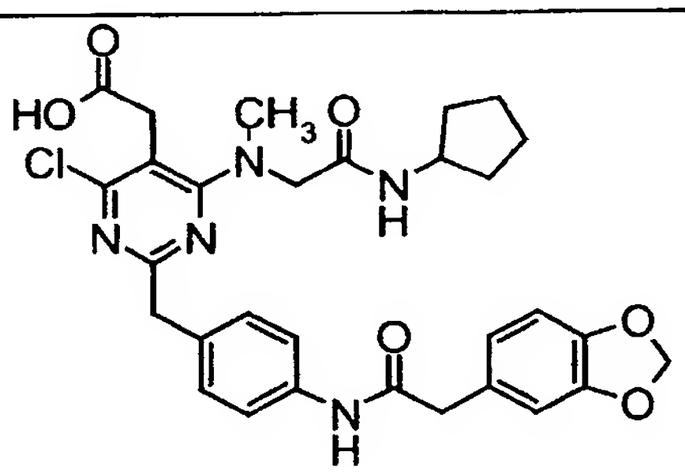
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-6		500,00	499	500	>146 Z	D
1-7		560,06	559	560	181 Z	A
1-8		600,12	599	600	134 Z	A
1-9		536,04	535	536	>140 Z	B

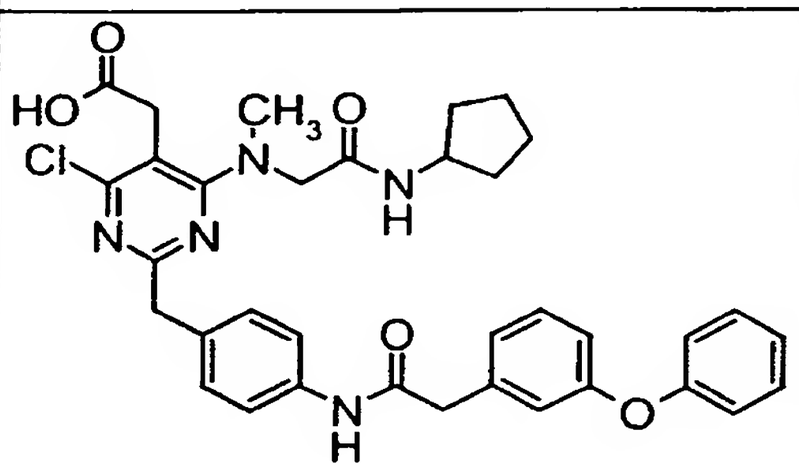
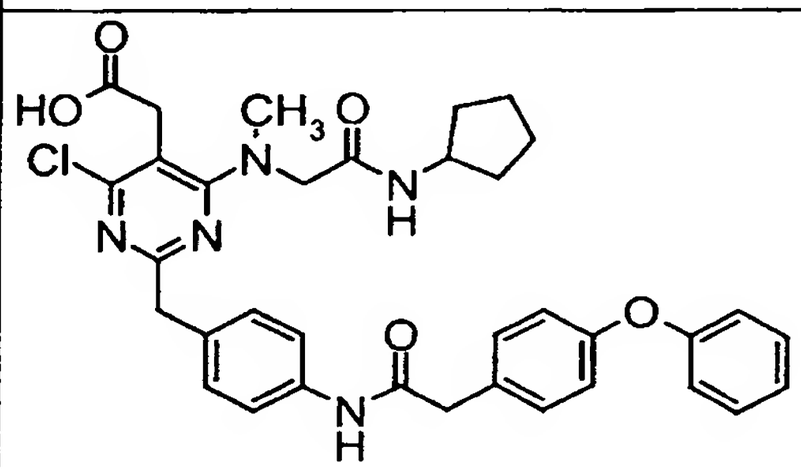
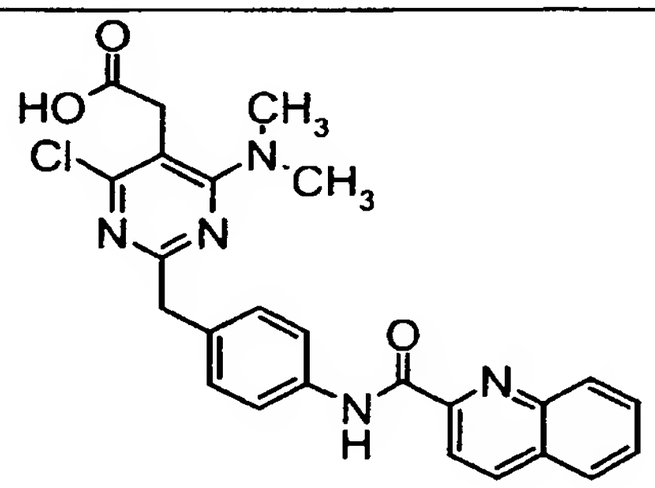
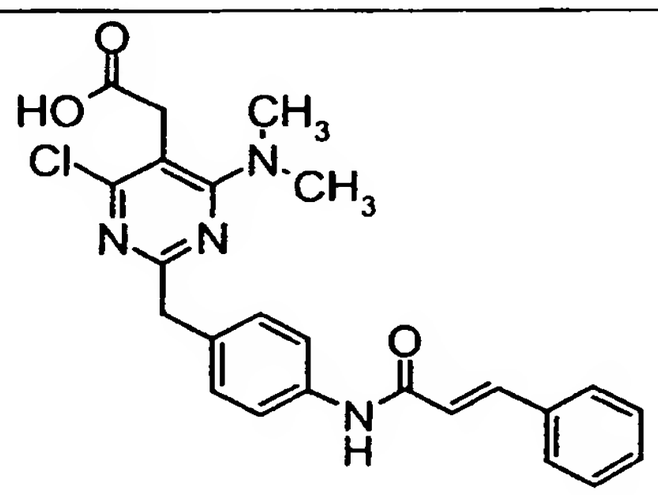
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-10		473,96	473	474	>118 Z	D
1-11		526,00	525	526	>119 Z	C
1-12		530,07	529	530	>100 Z	C
1-13		556,11	555	556	>149 Z	B

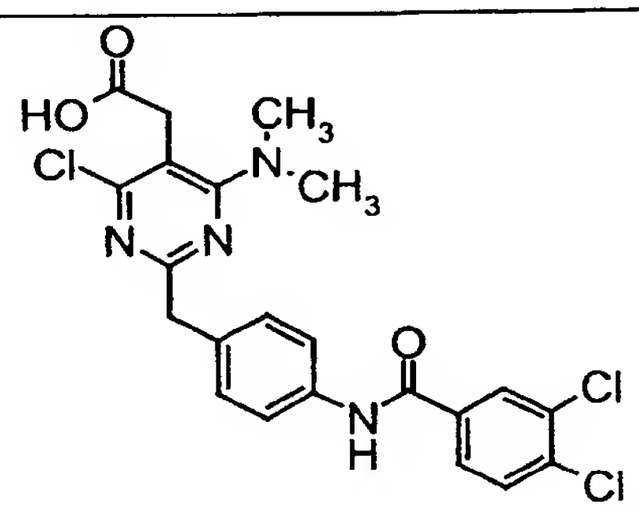
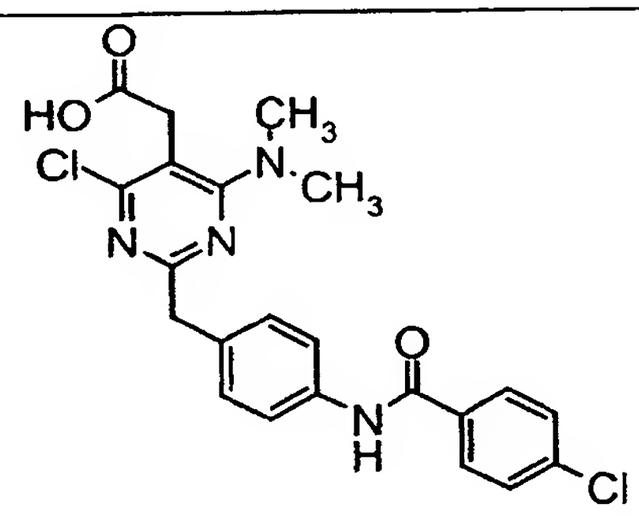
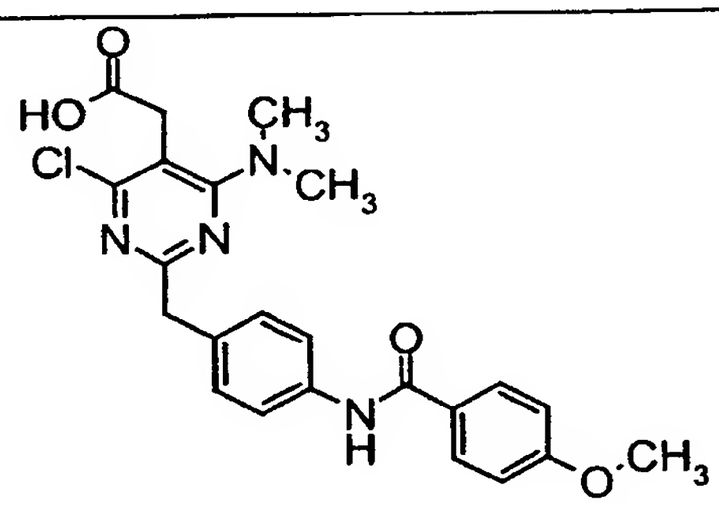
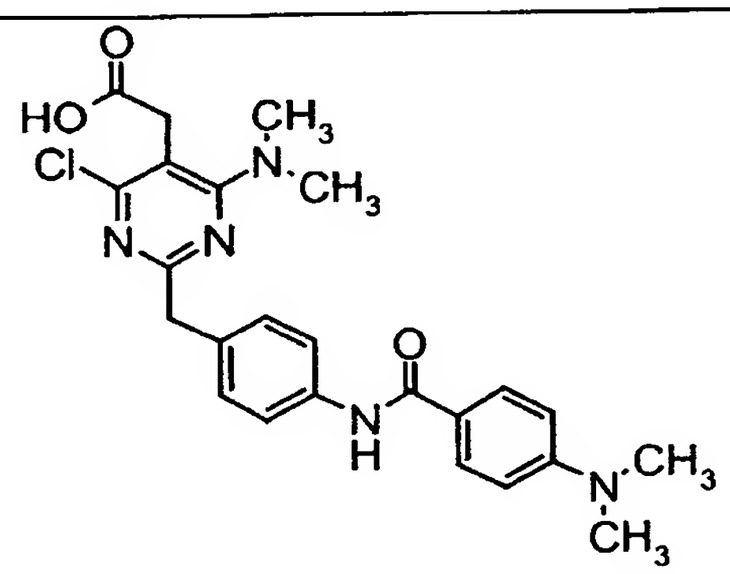
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-14		564,09	563	564	>139 Z	A
1-15		564,09	563	564	>116 Z	B
1-16		587,08	586	587	137 Z	A
1-17		562,07	561	562	142 Z	A

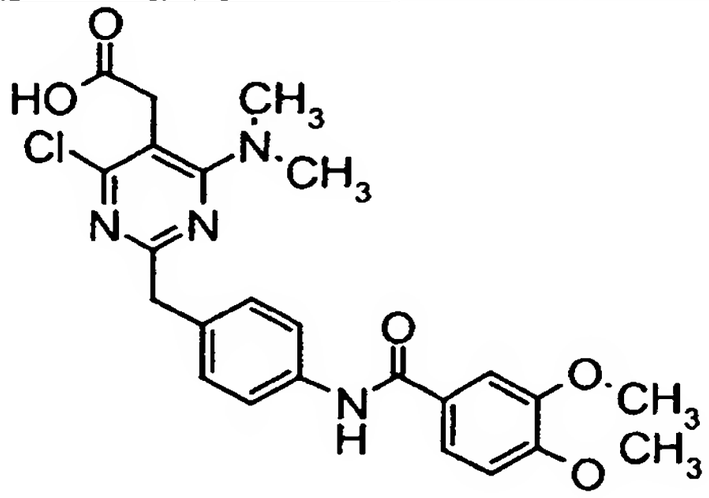
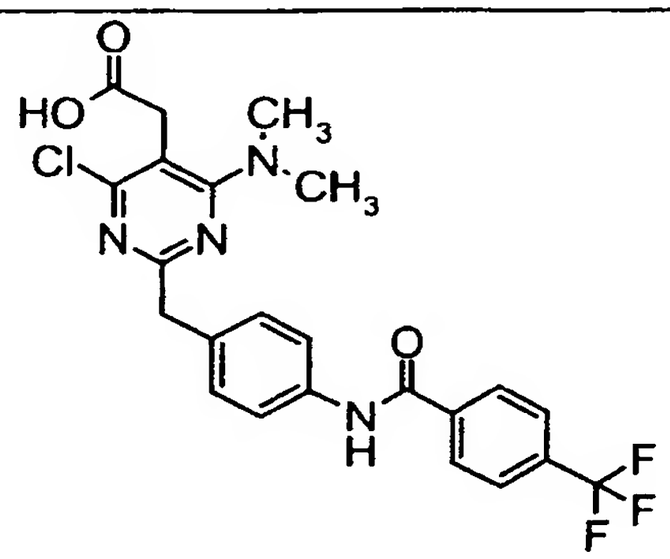
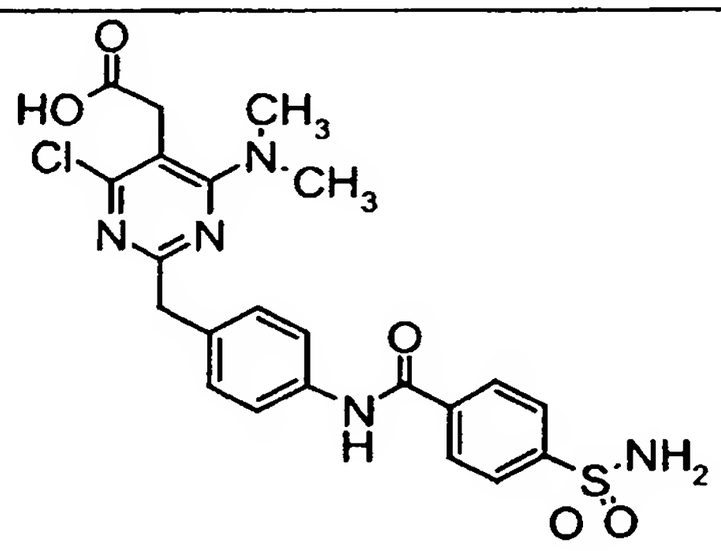
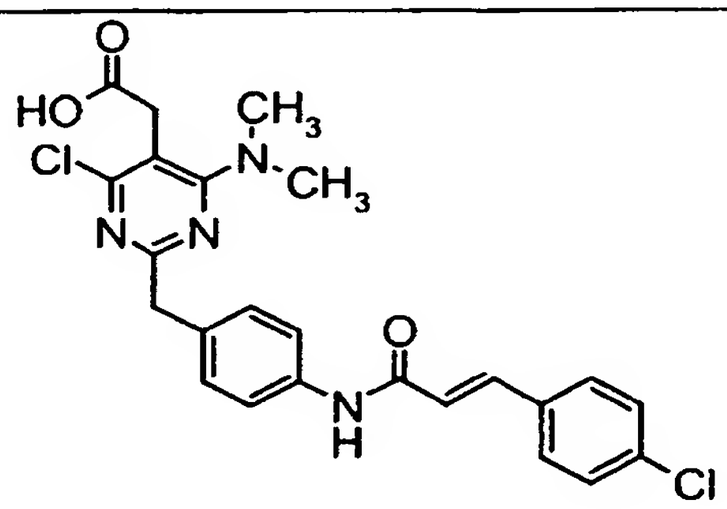
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-18		570,48	569	570	143 Z	A
1-19		604,93	603	604	144 Z	A
1-20		566,06	565	566	104 Z	A
1-21		550,06	549	550	125 Z	A

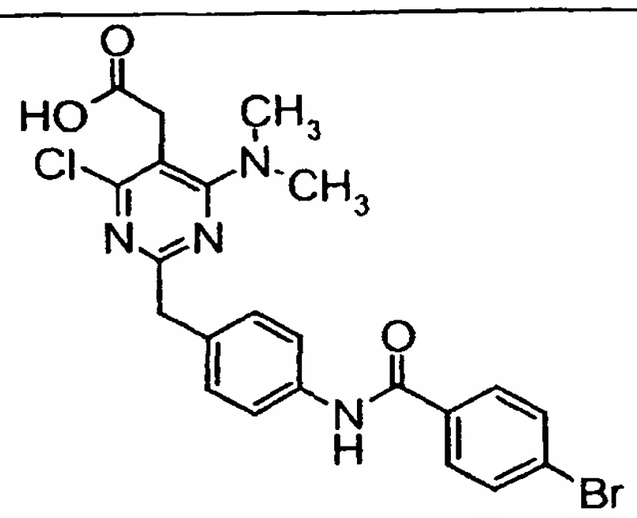
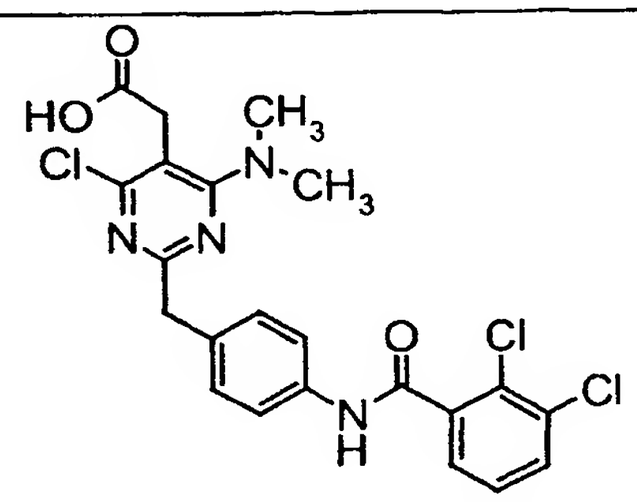
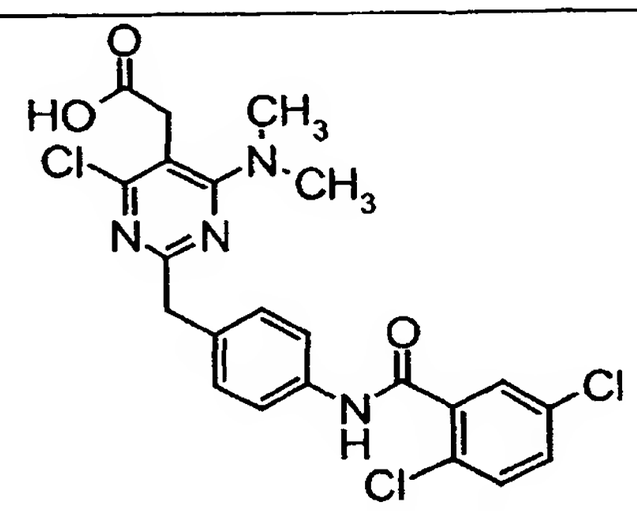
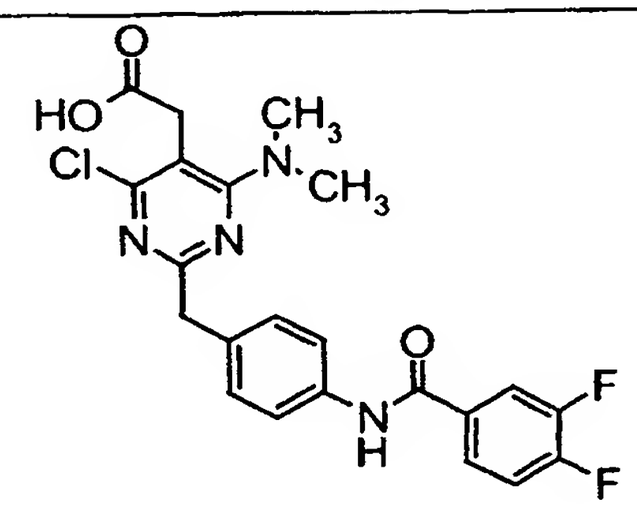
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-22		586,10	585	586	136 Z	B
1-23		622,15	621,00	622,00	116 Z	D
1-24		626,16	625,00	626,00	124 Z	C
1-25		576,06	575	576	118 Z	A

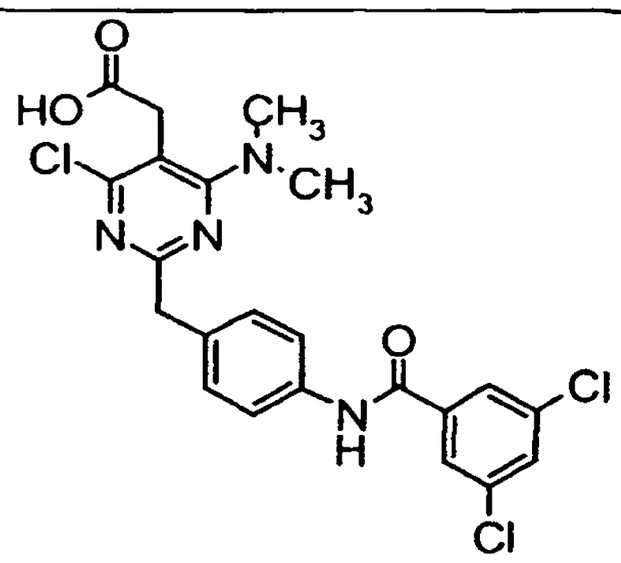
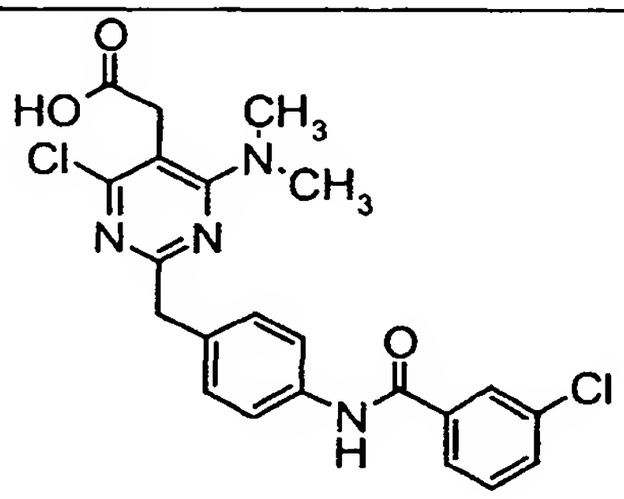
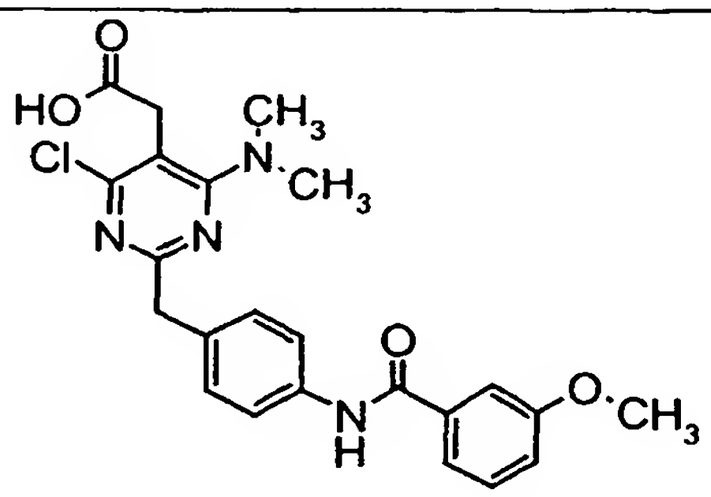
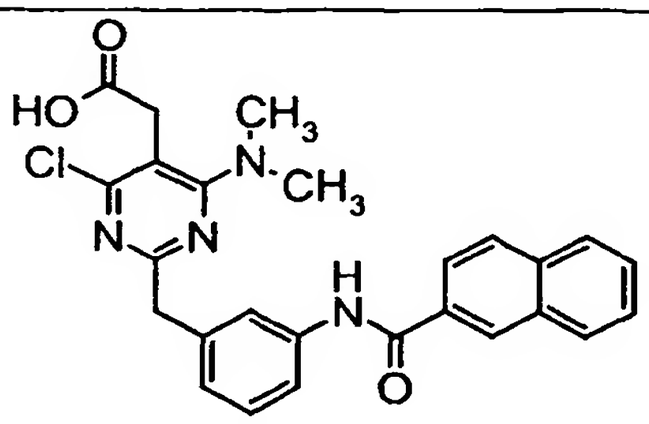
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-26		575,07	574	575	146 Z	A
1-27		561,05	560,00	561,00	101	A
1-28		590,13	589	590	>110 Z	A
1-29		594,07	593	594	>120 Z	C

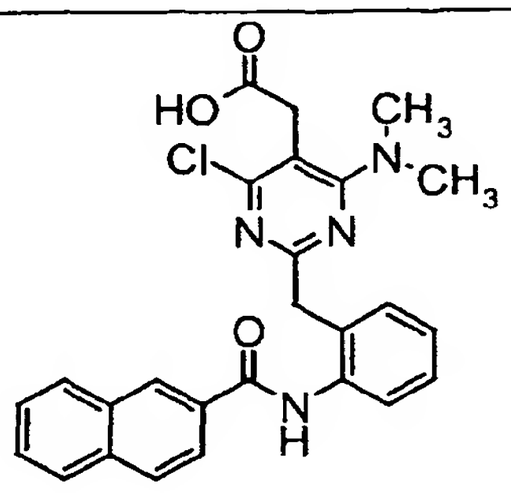
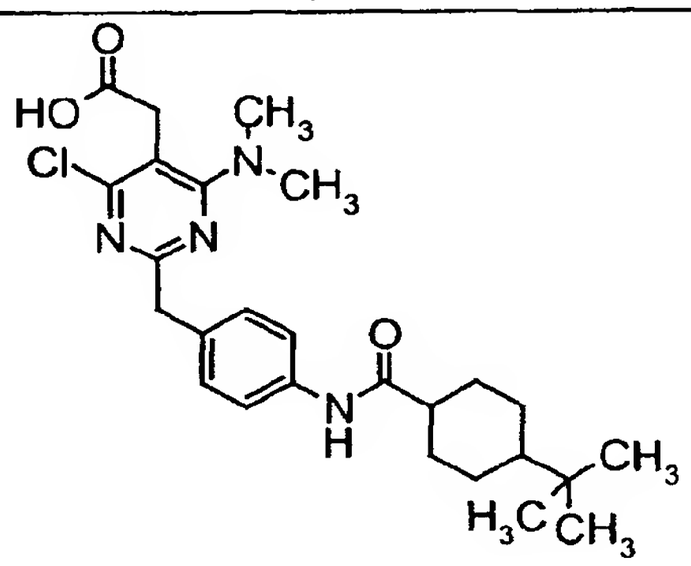
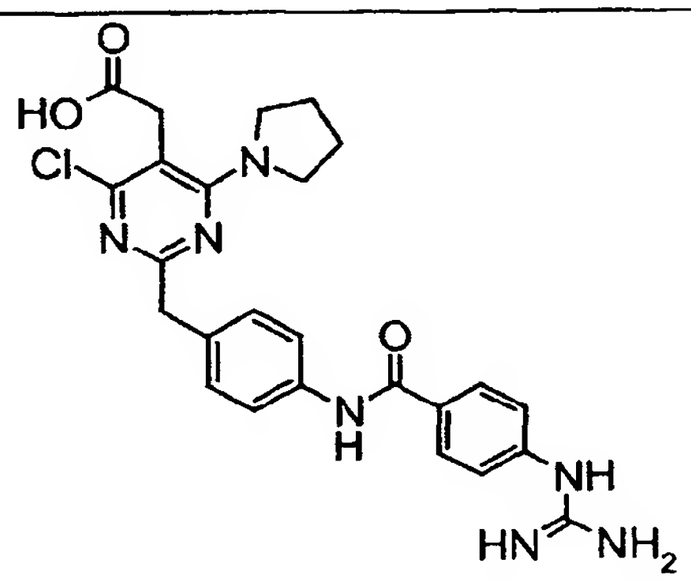
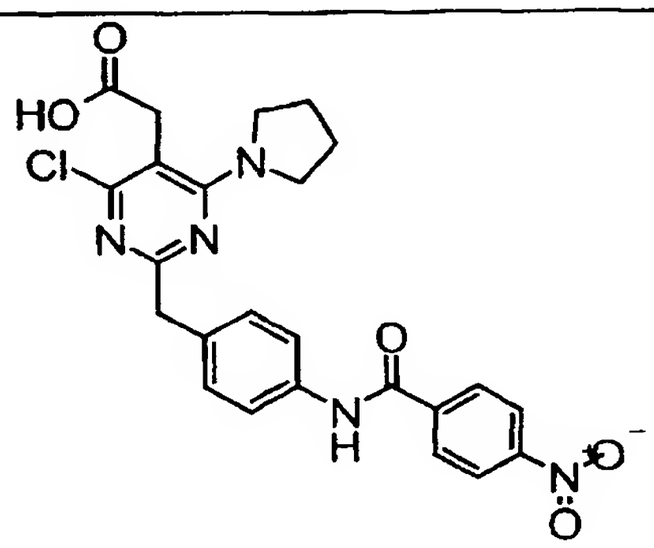
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-30		642,16	641	642	>118 Z	A
1-31		642,16	641	642	>123 Z	B
1-32		475,94	475	476	135-142	A
1-33		450,93	450	451	>160 Z	A

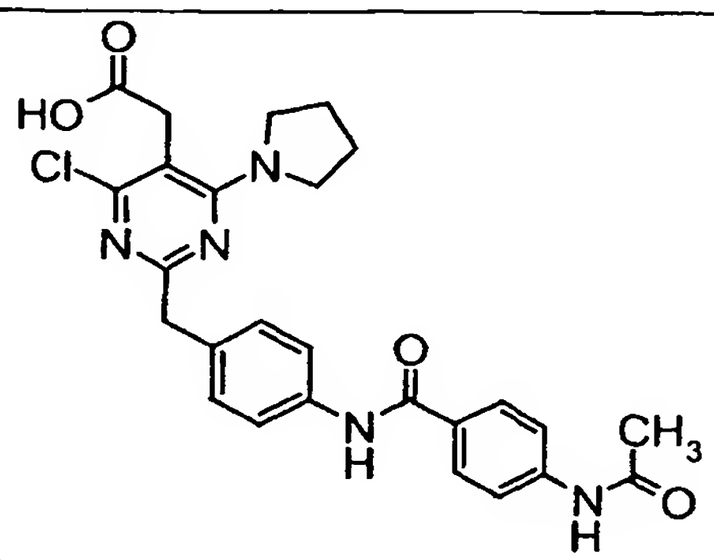
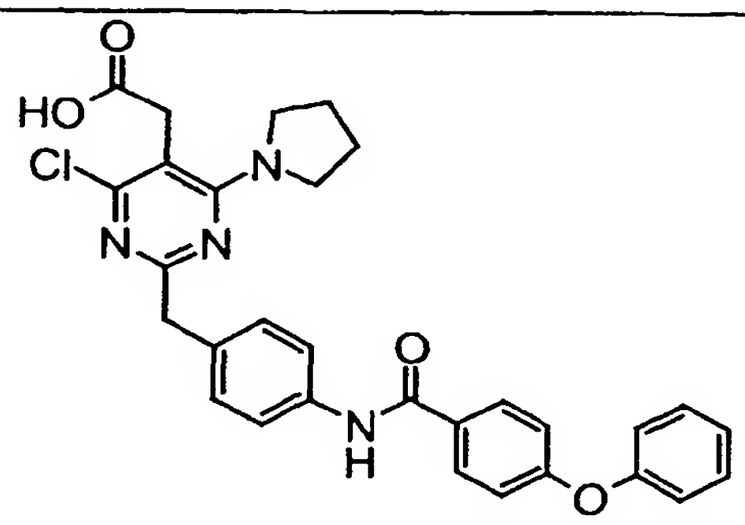
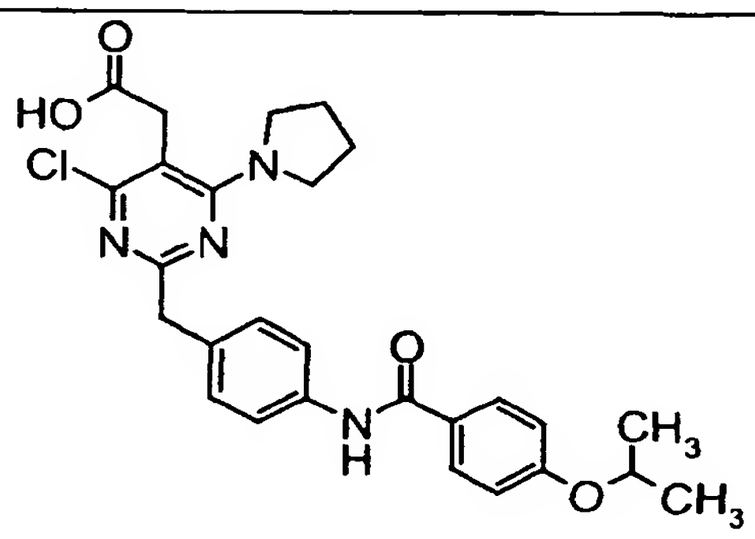
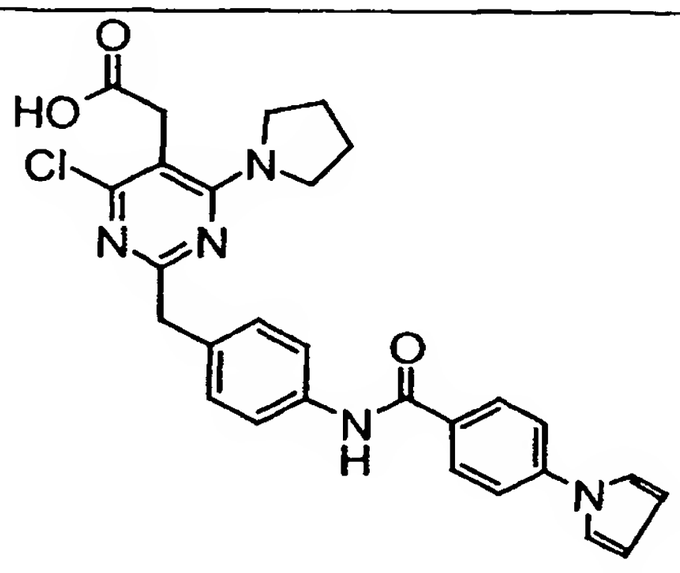
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-34		493,78	492	493	>168 Z	A
1-35		459,34	458	459	>166 Z	A
1-36		454,92	454	455	>130 Z	A
1-37		467,96	467	468	>111 Z	A

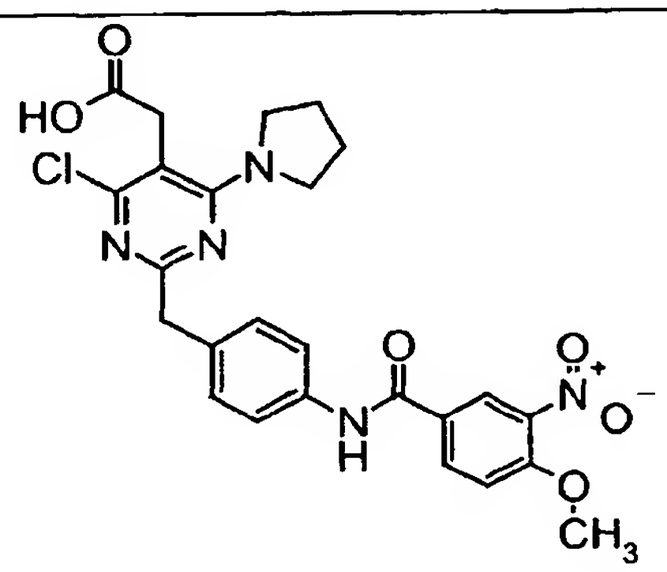
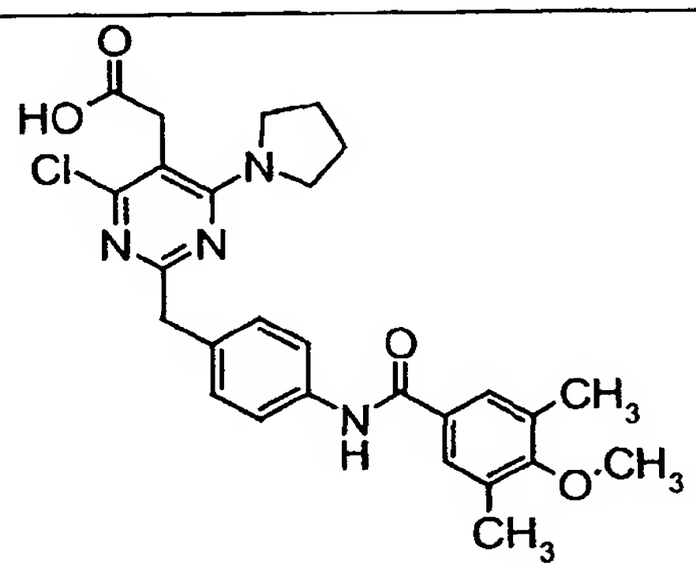
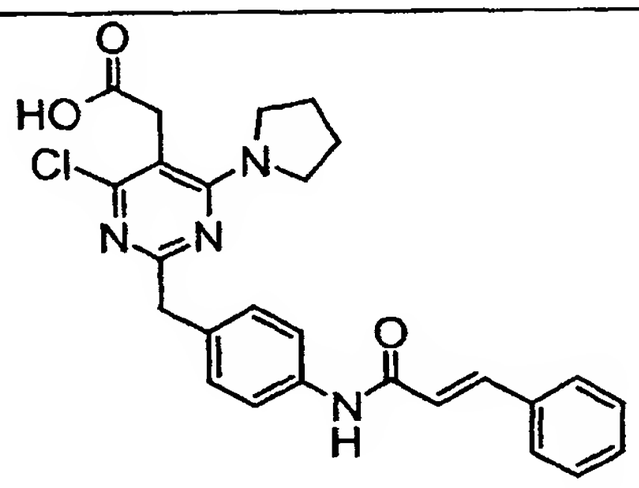
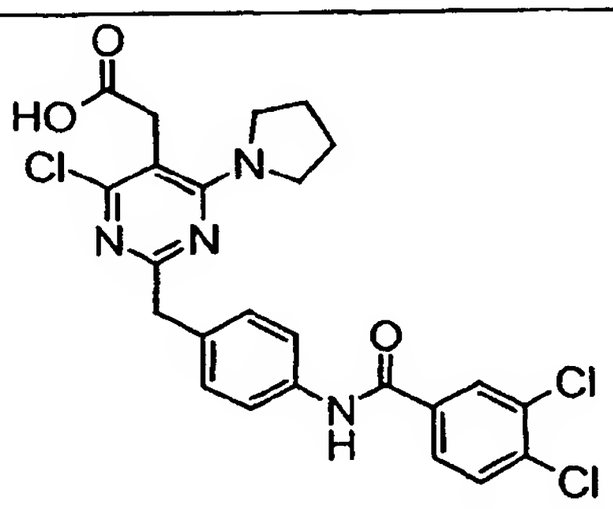
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-38		484,94	484	485	>95 Z	B
1-39		492,89	492	493	>150 Z	A
1-40		503,97	503	504	oil	C
1-41		485,37	484	485	117 Z	A

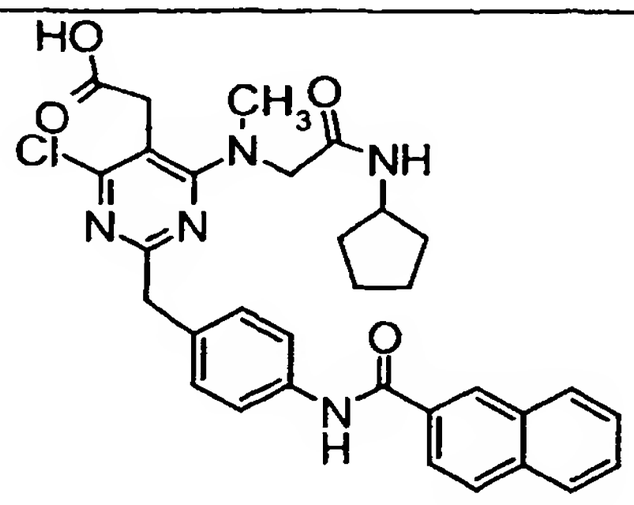
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-42		503,79	503	504	100 Z	A
1-43		493,78	492,00	493,00	101 Z	C
1-44		493,78	492	493	96 Z	A
1-45		460,87	460	461	>94 Z	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-46		493,78	492	493	>99 Z	A
1-47		459,34	458	459	>108 Z	A
1-48		454,92	454	455	>75	A
1-49		474,95	474	475	186	B

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-50		474,95	474	475	295 Z	D
1-51		487,05	486	487	104 Z	A
1-52		507,98	507	508	176	D
1-53		495,93	495	496	134 Z	B

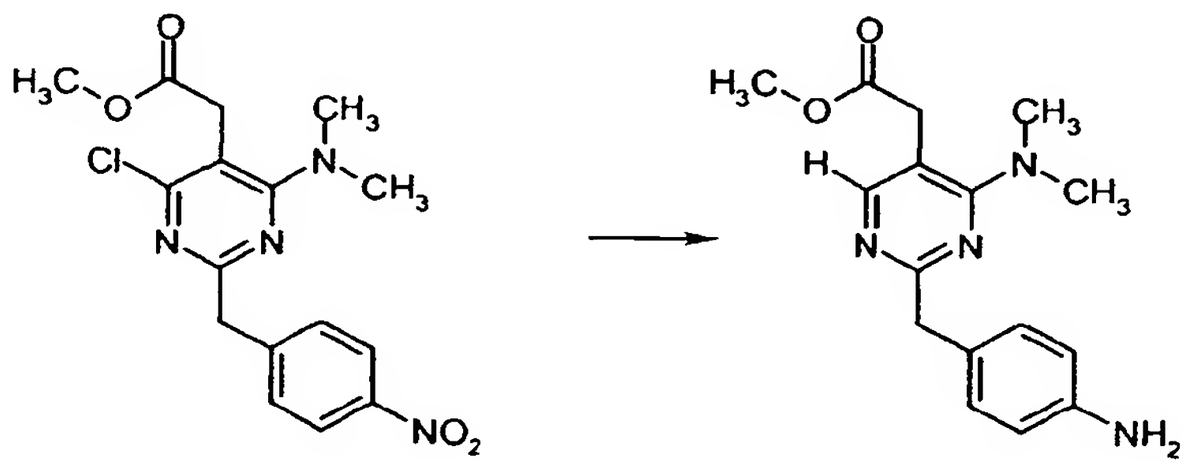
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-54		507,98	507,00	508,00	189 Z	B
1-55		543,03	542	543	160	A
1-56		509,01	508	509	156 Z	A
1-57		516,00	515	516	217 Z	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-58		525,95	525	526	118	A
1-59		509,01	508	509	115 Z	A
1-60		476,97	476	477	120 Z	A
1-61		519,82	518	519	129 Z	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
1-62		586,10	585	586	>176 Z	A

Methyl [2-(4-aminobenzyl)-4-(dimethylamino)-5-pyrimidinyl]acetate

[0152]

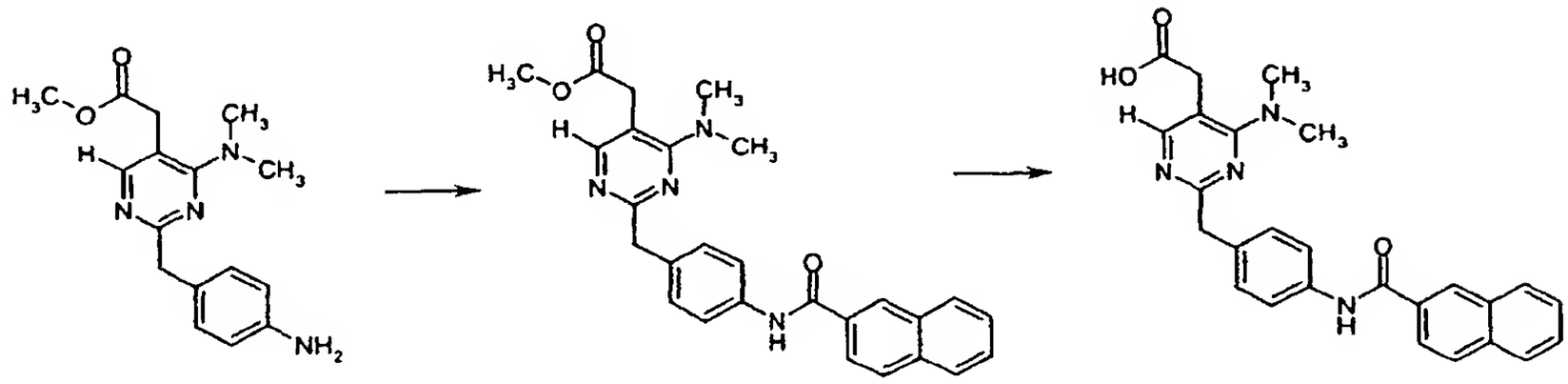


[0153] A suspension of methyl [4-chloro-6-(dimethylamino)-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (3.00 g, 8.22 mmol) and potassium acetate (2.42 g, 24.7 mmol) in methanol (30 mL) was treated with 10% Pd/C (1.00 g). The resulting black suspension was stirred under an atmosphere of hydrogen for 15 h and then filtered over Celite. The residue was rinsed with methanol and the filtrate concentrated to dryness before partitioning between EtOAc and water. The separated organic layer was sequentially washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatographic purification (silica gel, 1% MeOH in $CHCl_3$) of the thus obtained crude product then yielded methyl [2-(4-aminobenzyl)-4-(dimethylamino)-5-pyrimidinyl]acetate (2.40 g, 97% yield) as a brown oil.

Example 2-1

{4-(Dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid

[0154]



[0155] A solution containing methyl [2-(4-aminobenzyl)-4-(dimethylamino)-5-pyrimidinyl]acetate (0.090 g, 0.30 mmol) and PyBOP (0.187 g, 0.36 mmol) in anhydrous DMF (1 mL) at r.t. was treated with 2-naphthoic acid (0.062 g, 0.36 mmol). The reaction mixture was stirred for 3 h before diluting with water. The thus quenched reaction mixture was extracted with EtOAc and the combined organic extracts was washed sequentially with 0.5N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to give the crude product methyl {4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate.

[0156] The thus obtained methyl {4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate was dissolved in THF (6 mL) and treated with 1N NaOH (3 mL). The biphashic reaction mixture was stirred at r.t. for 14 h and then Et_2O was added. The organic layer was siphoned off and the remaining aqueous layer was neutralized with 6N HCl. The separated solids was collected by suction, triturated with diisopropyl ether, and filtered to give {4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid (0.047 g, 36% yield).

[0157] ^1H NMR (500 MHz, DMSO-d_6) δ: 3.04 (s, 6H), 3.65 (s, 2H), 3.93 (s, 2H), 7.32 (d, J=9 Hz, 2H), 7.60-7.66 (m, 2H), 7.73 (d, J=9 Hz, 2H), 7.97 (s, 1H), 8.00-8.09 (m, 4H), 10.35 (s, 1H), 12.54 (s, 1H).

Molecular weight: 440.51

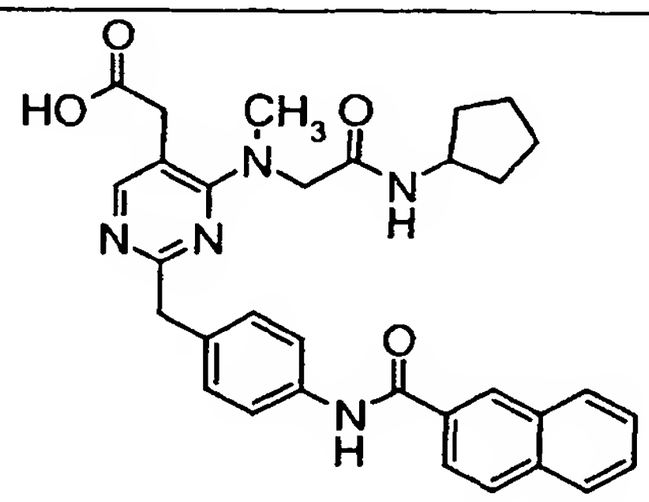
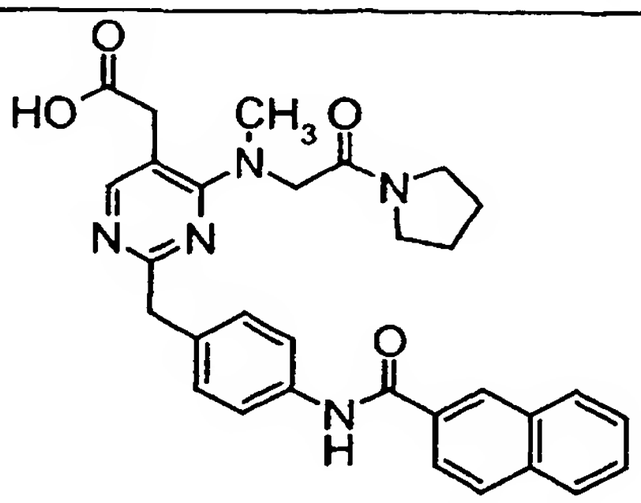
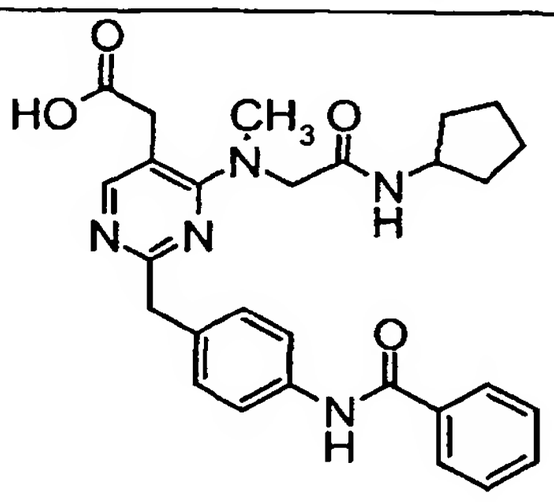
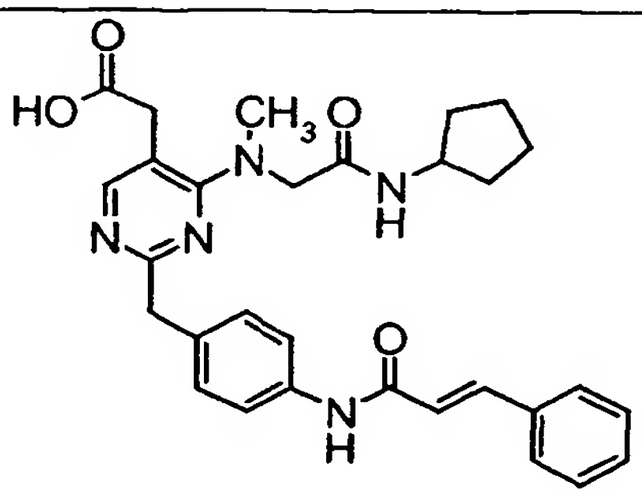
Mass spectrometry: 441

Melting point: 210°C

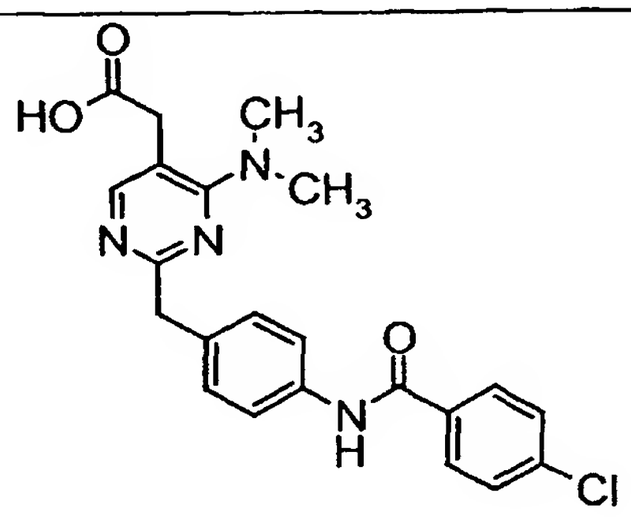
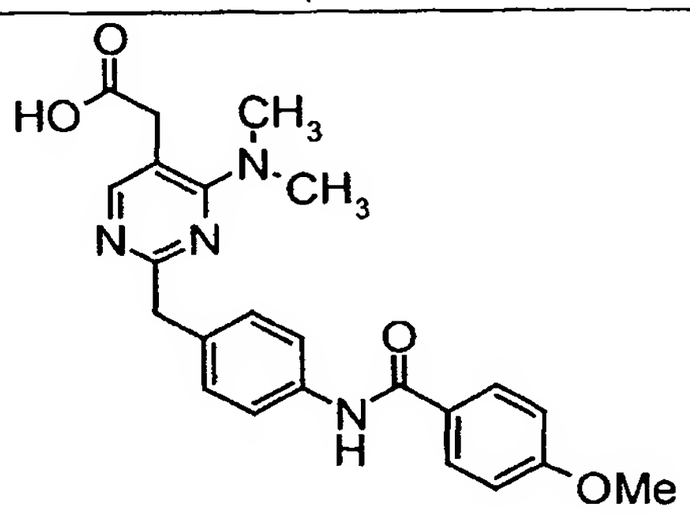
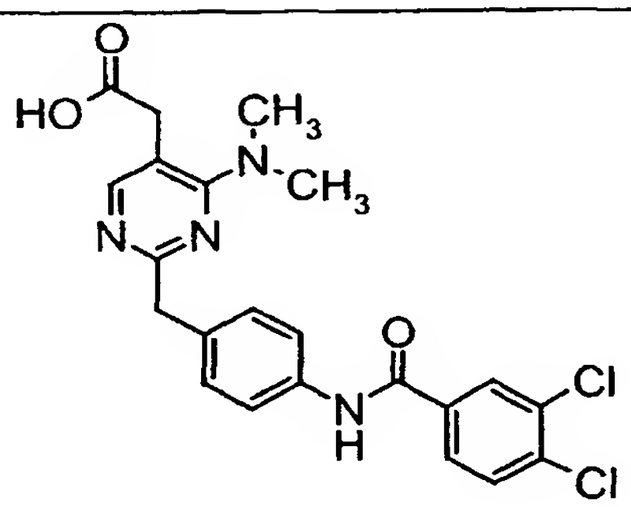
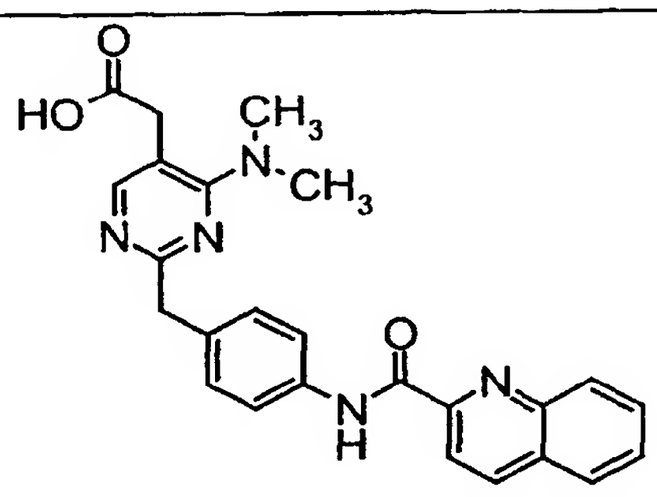
Activity class: A

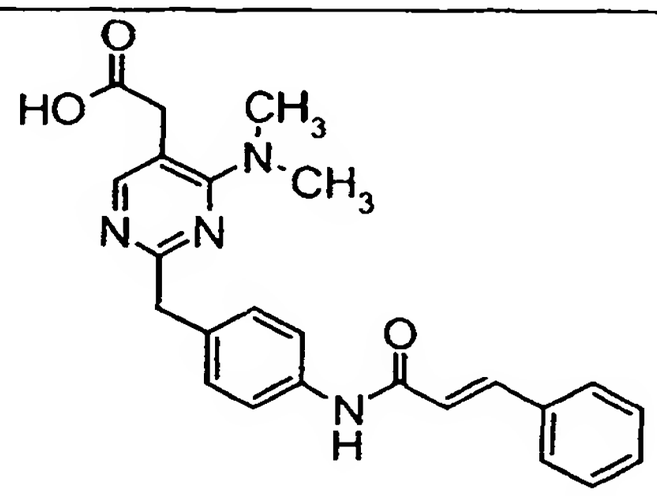
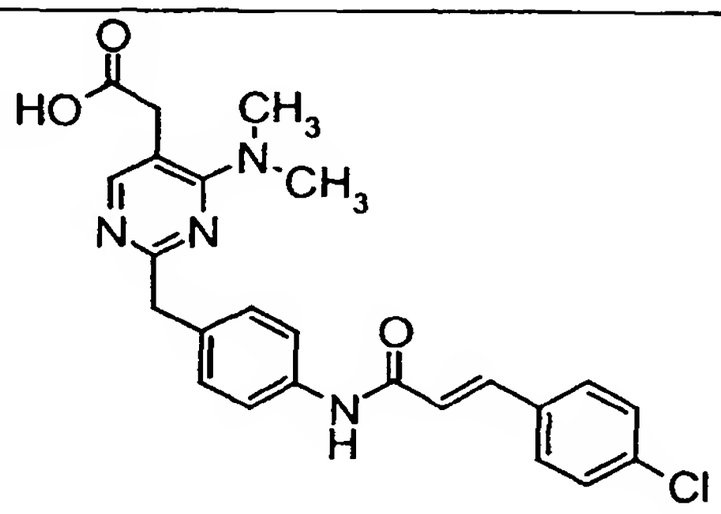
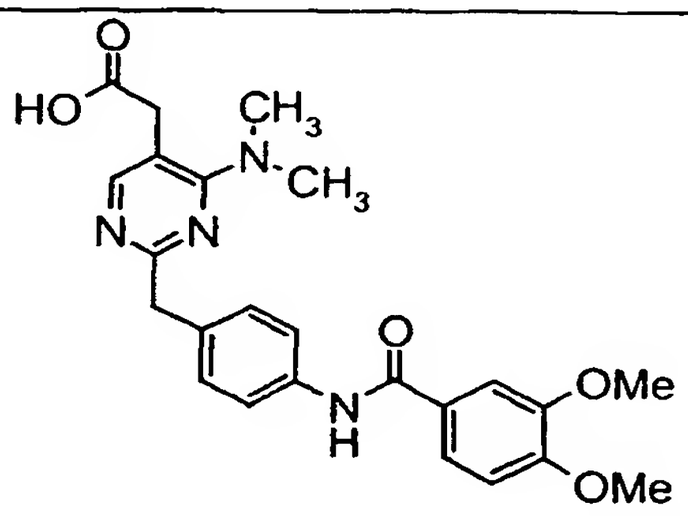
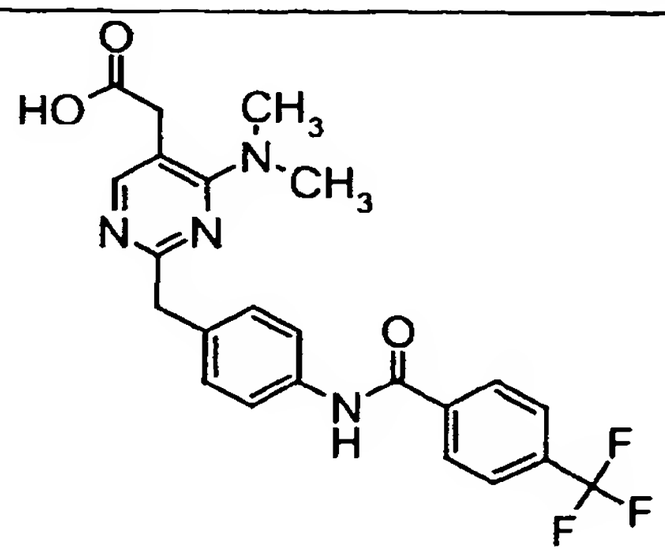
[0158] In a similar manner as described in Example 2-1, compounds in Example 2-2 to 2-16 as shown in Table 2 were synthesized.

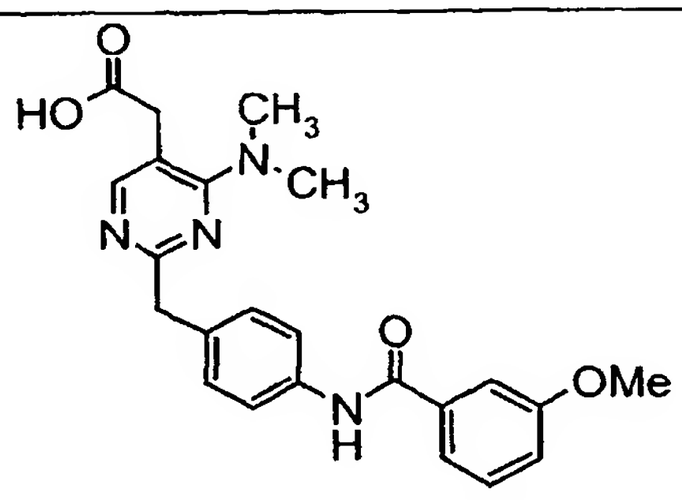
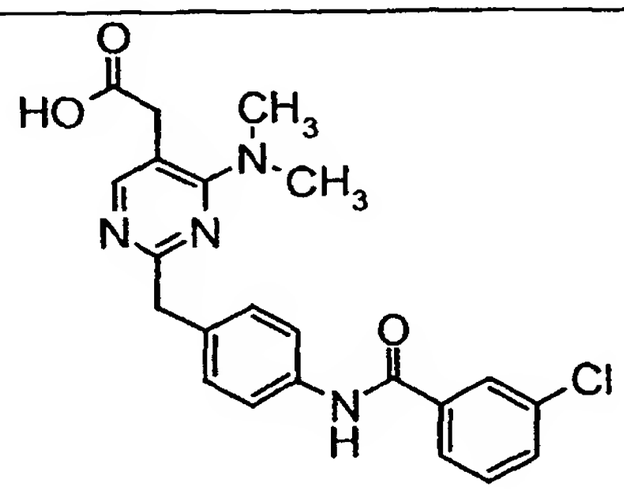
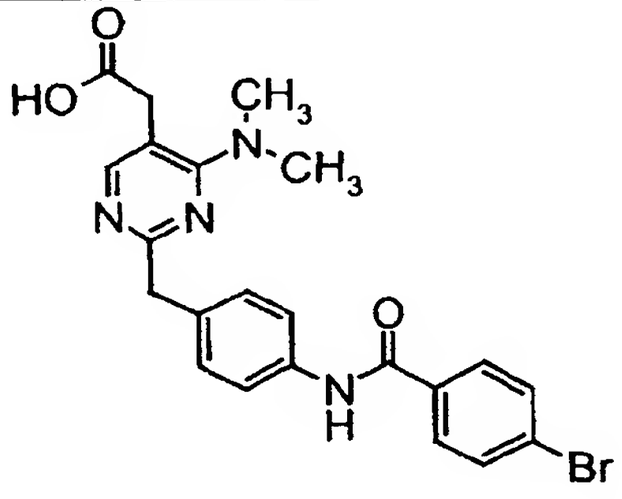
Table 2

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
2-2		551,64	551	552	287 Z	A
2-3		537,62	537	538	201 Z	A
2-4		501,59	501,00	502,00	212 Z	B
2-5		527,63	527,00	528,00	209 Z	A

:NSDOCID: <EP_____1471057A1_I_>

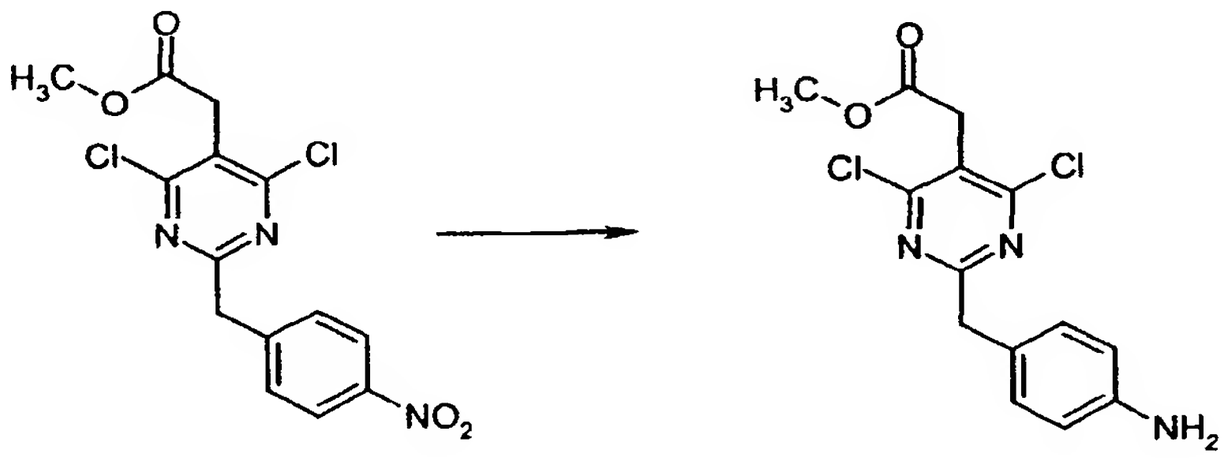
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
2-6		424,89	524,00	525,00	147	A
2-7		420,47	420,00	421,00	111	A
2-8		459,34	458,00	459,00	140	A
2-9		441,49	441,00	442,00	136-144	B

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
2-10		416,48	416,00	417,00	135-140	A
2-11		450,93	450	451	136-140	A
2-12		450,50	450,00	451,00	106-110	C
2-13		458,44	458	459	149-153	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
2-14		420,47	420,00	421,00	94 Z	B
2-15		424,89	424,00	425,00	111-113	B
2-16		469,34	469	470	220 Z	A

Methyl [2-(4-aminobenzyl)-4,6-dichloro-5-pyrimidinyl]acetate

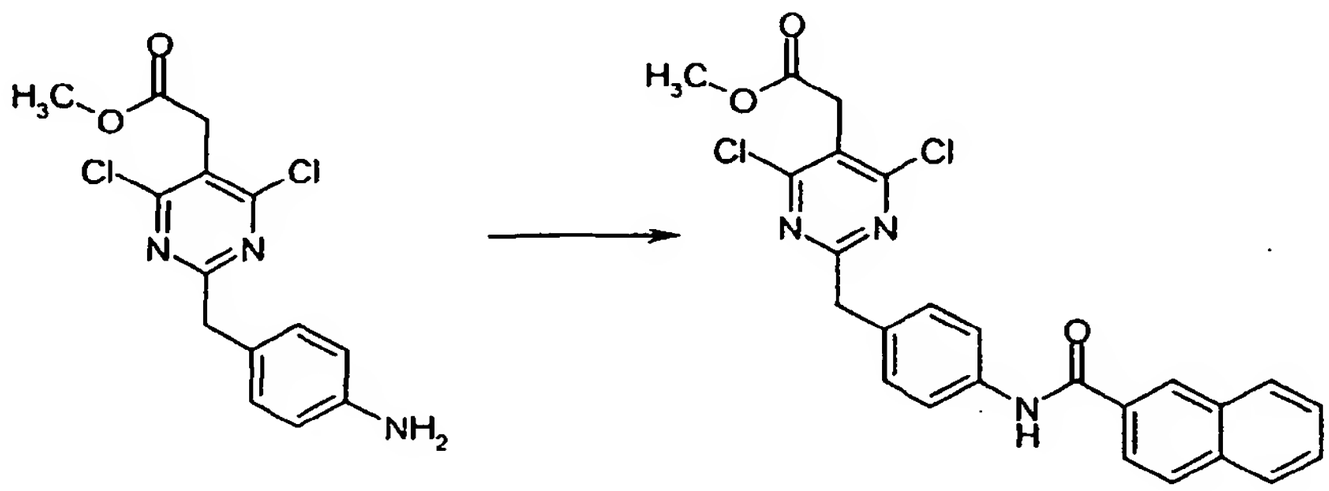
[0159]



[0160] A solution of methyl [4,6-dichloro-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (2.00 g, 5.62 mmol) in anhydrous THF (50 mL) was treated with Pd/C (10% Pd, 0.200 g) and the resulting black suspension was stirred under an atmosphere of hydrogen at r.t. After 16 h, the reaction mixture was filtered over Celite and the residue rinsed with copious amounts of MeOH. The filtrate was concentrated *in vacuo* to give the crude product as a dark yellow oil which was chromatographed (silica gel, 40% EtOAc in *n*-hexane) to give methyl [2-(4-aminobenzyl)-4,6-dichloro-5-pyrimidinyl] acetate (1.32 g, 72% yield) as a white powder.

Methyl {4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate

[0161]

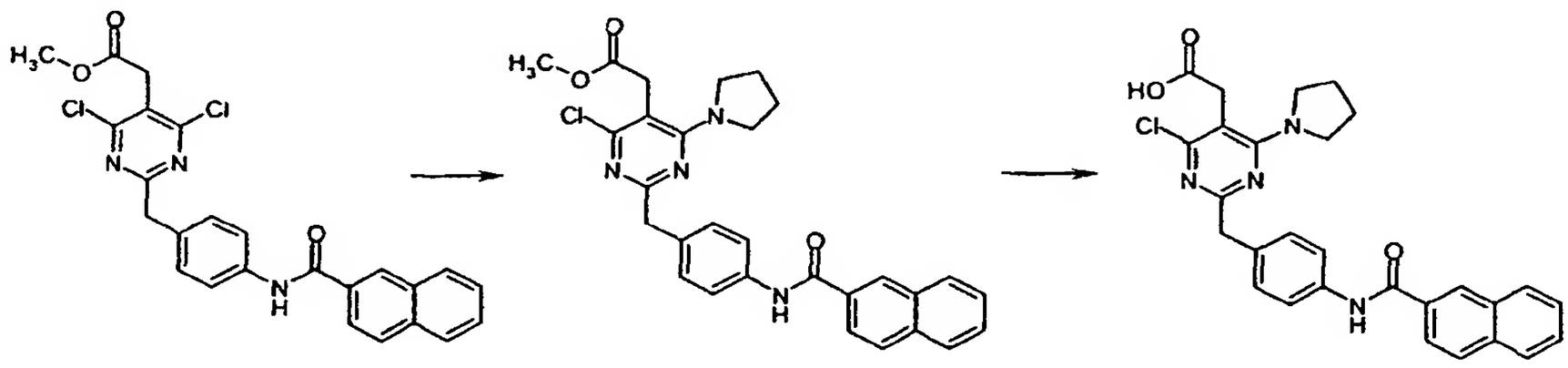


[0162] A mixture of methyl [2-(4-aminobenzyl)-4,6-dichloro-5-pyrimidinyl]acetate (0.073g, 0.23 mmol), 2-naphthoic acid (0.048 g, 0.028 mmol), and WSCI (0.049 g, 0.026 mmol) in anhydrous THF (3 mL) was stirred at r.t. under Ar atmosphere for 10 h. EtOAc (80 mL) was then introduced and the organic phase was washed sequentially with saturated $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product thus obtained as a light orange oil was triturated with diisopropyl ether and the separated solids was collected by suction to give methyl {4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate (0.090 g, 78% yield) as a white powder.

Example 3-1

[4-Chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid

[0163]



[0164] A mixture of methyl {4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate (0.100 g, 0.21 mmol), pyrrolidine (0.019 mL, 0.23 mmol), and *N,N*-diisopropylethylamine (0.109 mL, 0.62 mmol) in anhydrous DMF (2 mL) was stirred at 80 °C for 5 h. After cooling to r.t., the solvent was evaporated and the remaining residue dissolved in EtOAc. This organic solution was sequentially washed with 1N HCl, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo.* Purification by preparative TLC then afforded methyl [4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.100 g, 95% yield) as a white powder.

[0165] A solution of methyl [4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.085 g, 0.17 mmol) in THF (3 mL) was treated with 1N NaOH (1.5 mL) and the biphasic mixture was stirred at r.t. for 45 h. Et_2O was then added and the organic layer siphoned off. The remaining aqueous layer was cooled to 0 °C and acidified

with 6N HCl. The separated solids were collected by suction and rinsed with water. Drying under high vacuum at 45 °C for 5 h gave [4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid (0.050 g, 56% yield) as an off-white powder.

[0166] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.86 (bs, 4H), 3.59 (bs, 4H),3.78 (s, 2H), 3.88 (s, 2H), 7.32 (d, J=9 Hz, 2H), 7.63 (m, 2H), 7.96-8.13 (m, 4H), 8.57 (s, 1H), 10.39 (s, 1H), 12.72 (s, 1H).

Molecular weight: 500.99

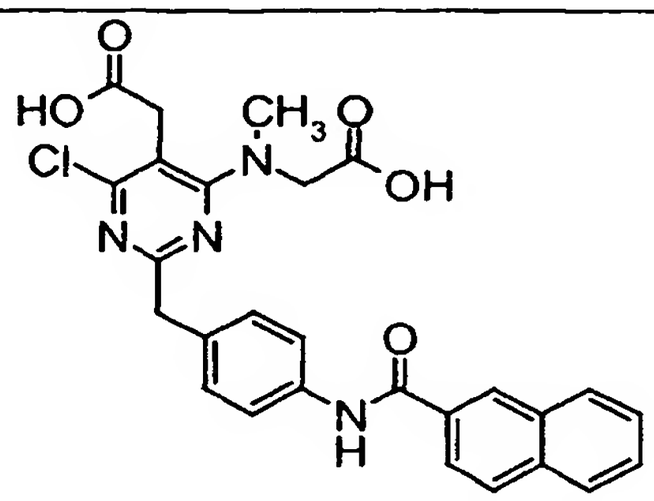
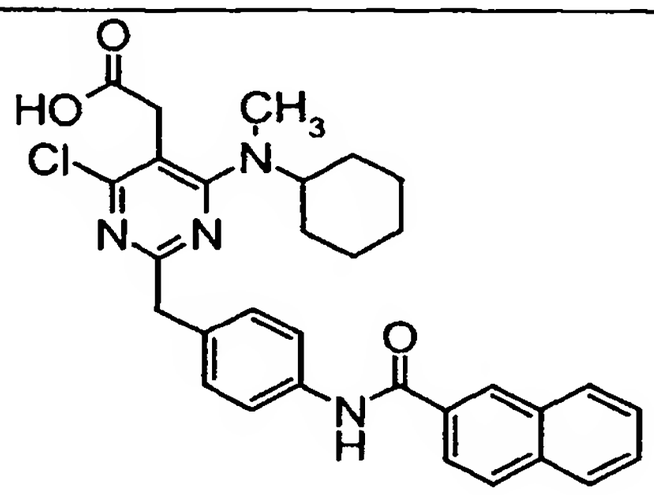
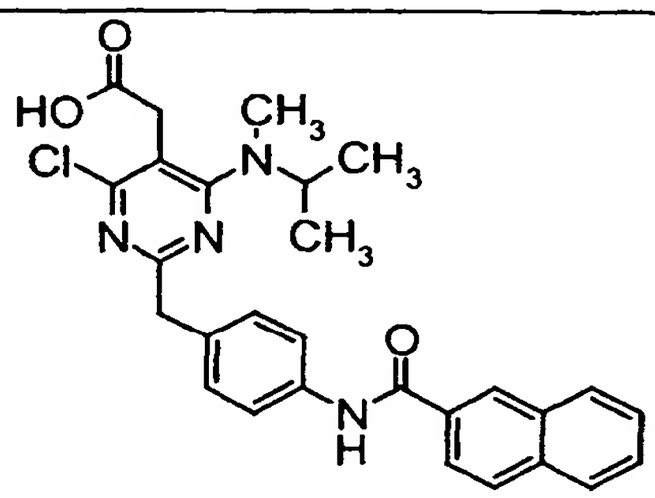
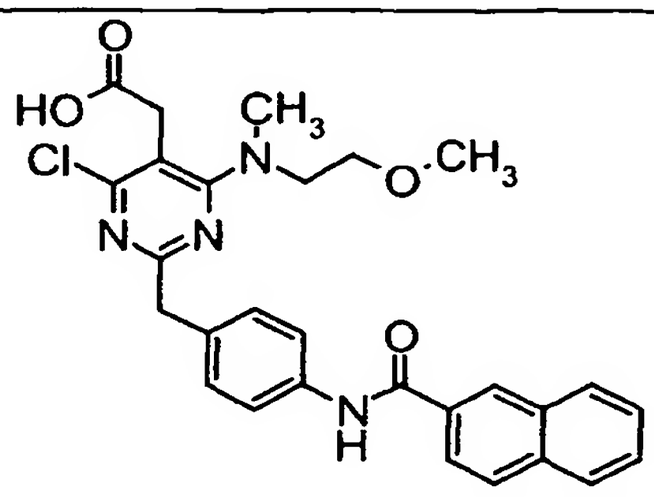
Mass spectrometry: 501

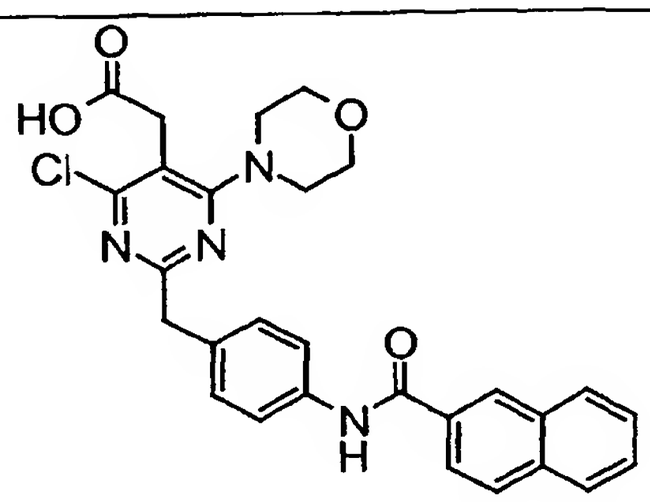
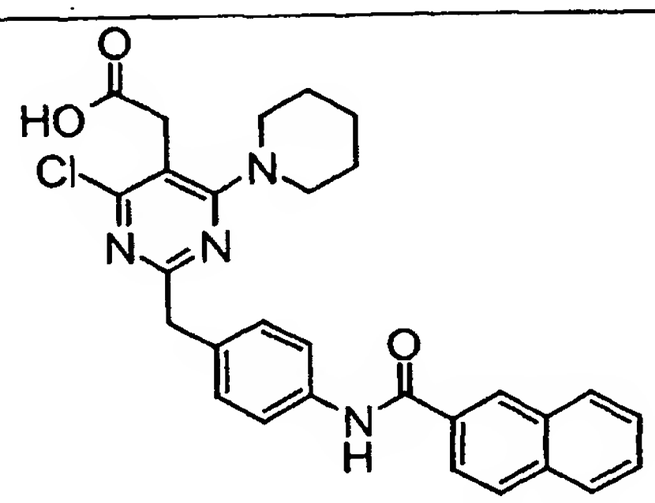
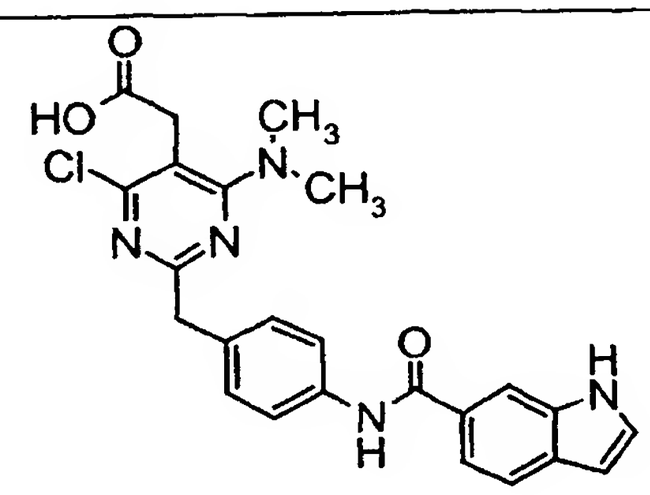
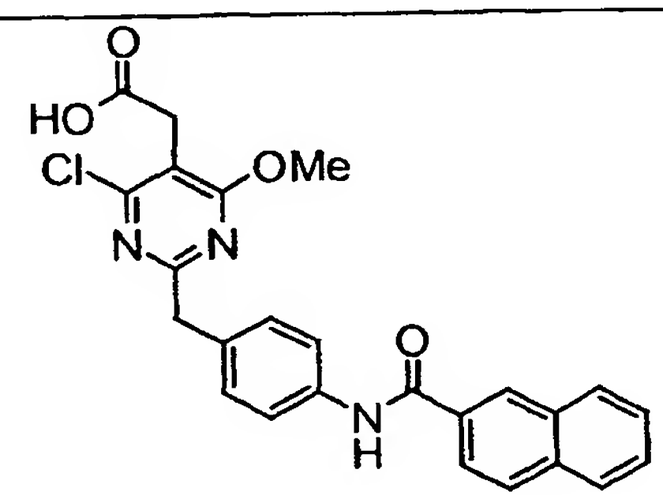
Melting point: 196 Z °C

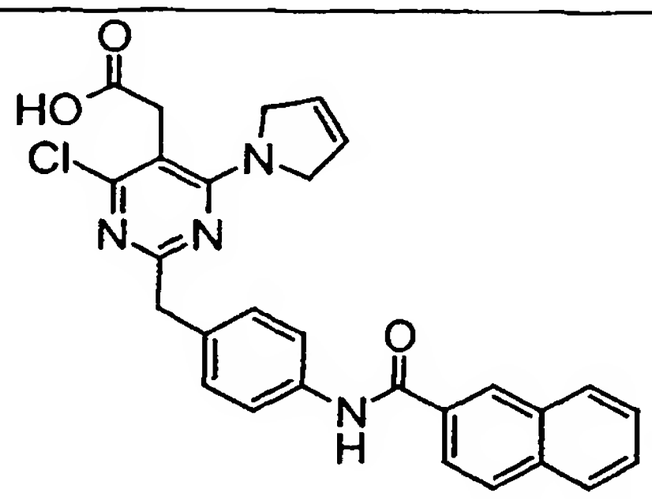
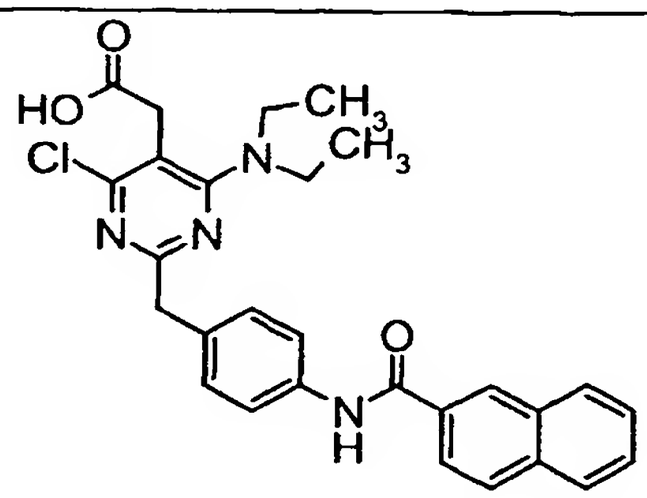
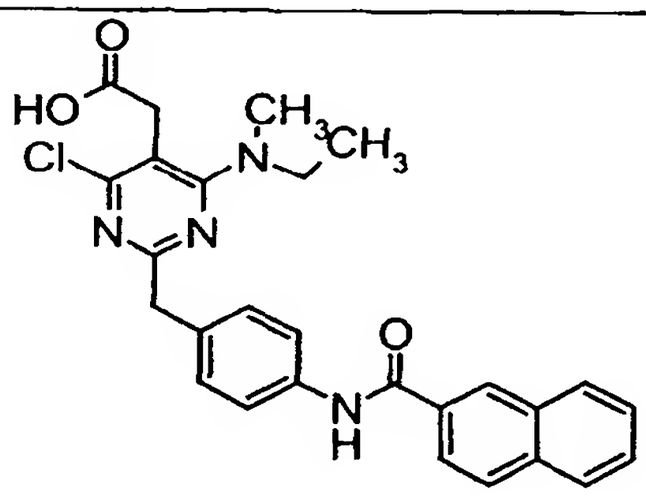
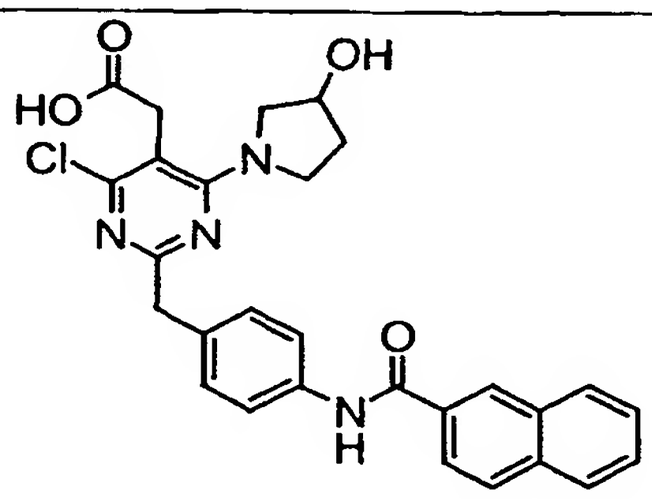
Activity class: A

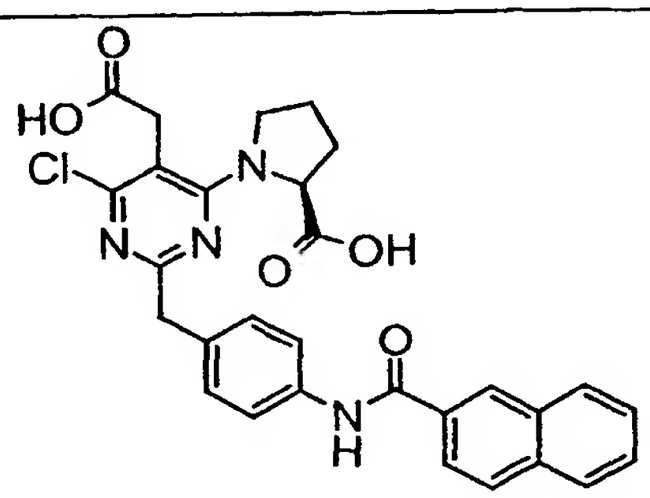
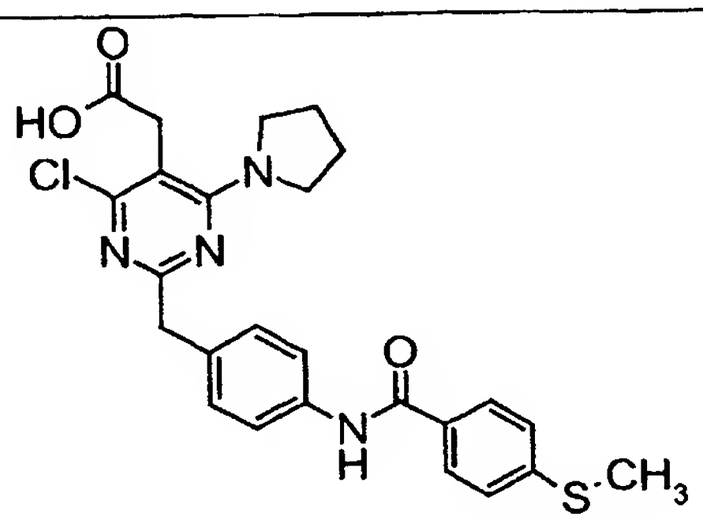
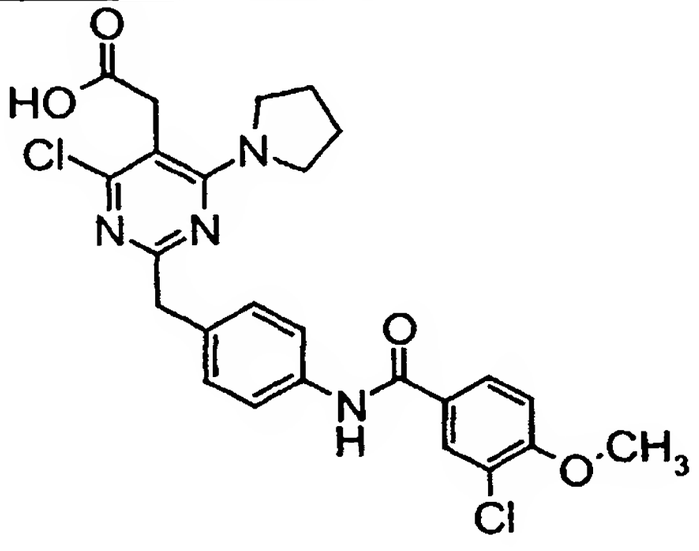
[0167] In a similar manner as described in Example 3-1, compounds in Example 3-2 to 3-16 as shown in Table 3 were synthesized.

Table 3

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
3-2		518,96	518	519	176 Z	B
3-3		543,07	542	543	185 Z	A
3-4		503,01	502	503	132 Z	A
3-5		519,00	518	519	144	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
3-6		516,99	516	517	172 Z	A
3-7		515,02	514	515	157 Z	A
3-8		463,93	463	464	>165 Z	A
3-9		461,91	461	462	201 Z	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
3-10		498,97	498	499	>146 Z	A
3-11		503,01	502	503	>90 Z	B
3-12		488,98	488	489	>125 Z	A
3-13		516,99	516	517	>202 Z	A

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
3-14		545,00	544	545	>174 Z	B
3-15		497,02	496	497	157 Z	A
3-16		515,40	514	515	108 Z	A

Example 4-1

{2-{4-[(Anilinocarbonyl)amino]benzyl}-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid

[0168] A solution of methyl [2-(4-aminobenzyl)-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl]acetate (0.050 g, 0.11 mmol) in DMF (2 mL) was treated with phenyl isocyanate (0.022 mL, 0.20 mmol). After stirring at r.t. for 18 h, EtOAc was added and the organic phase was washed with 8% $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude product thus obtained was triturated with CH_2Cl_2 and diisopropyl ether to give methyl {4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(3-phenylureido)benzyl]-5-pyrimidinyl)acetate (0.055 g, 87% yield) as a white powder.

[0169] To a solution of methyl {4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(3-phenylureido) benzyl]-5-pyrimidinyl}acetate (0.047 g, 0.083 mmol) in THF (3 mL) was added 1N NaOH (1.5 mL) and the biphasic mixture was stirred at r.t. for 18 h. Et_2O was added and the separated organic layer siphoned off. The remaining

aqueous layer was acidified with 6N HCl and the separated solids were collected by suction and rinsed with water and diisopropyl ether. Drying under high vacuum for 5 h gave {2-{4-[(anilinocarbonyl)amino]benzyl}-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid (0.026 g, 56% yield) as a white powder.

[0170] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.26-1.82 (m, 8H), 3.08 (s, 3H), 3.69 (s, 2H), 3.81 (s, 2H), 3.98 (s, 2H), 4.00-4.18 (m, 1H), 6.95 (t, J=7 Hz, 1H), 7.20 (d, J=9 Hz, 2H), 7.27 (t, J=8 Hz, 2H), 7.35 (d, J=9 Hz, 2H), 7.43 (d, J=8 Hz, 2H), 7.94 (d, J=7 Hz, 1H), 8.61 (d, J=5 Hz, 2H), 12.76 (bs, 1H).

Molecular weight: 551.05

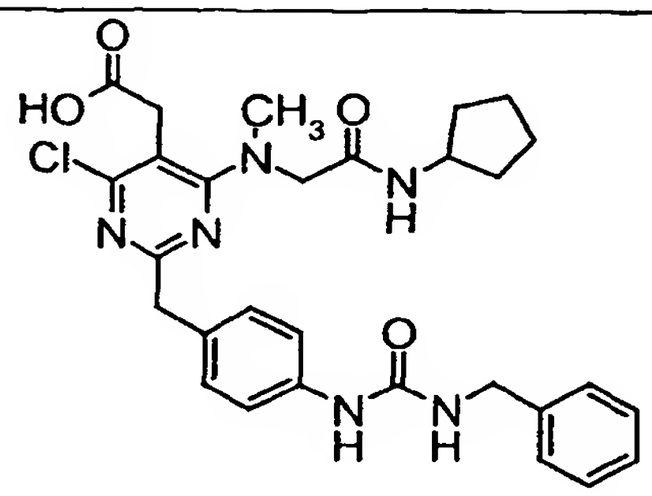
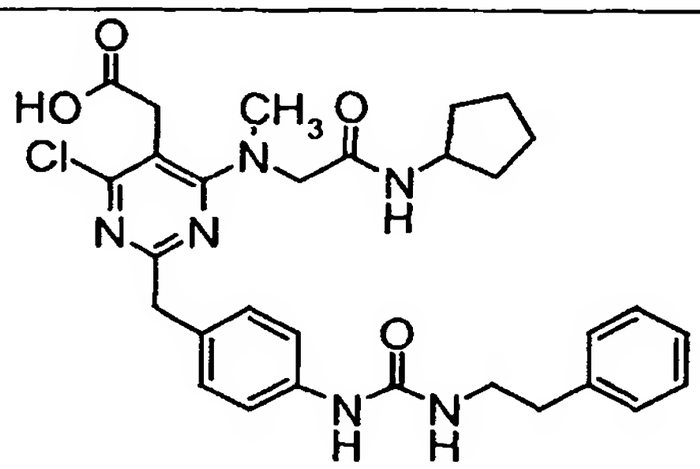
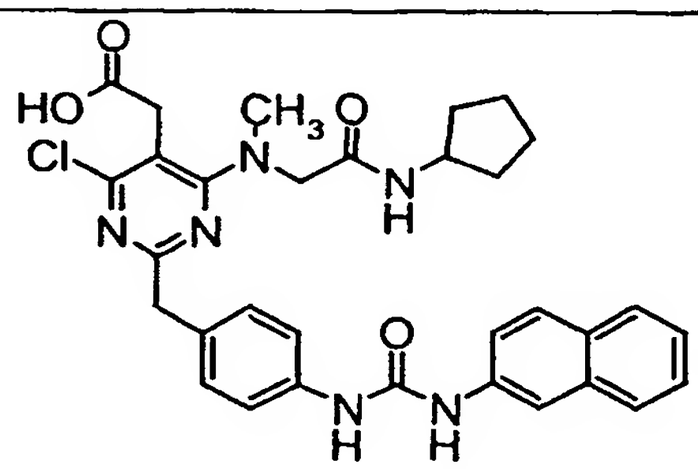
Mass spectrometry: 551

Melting point: >153 Z °C

Activity class: B

[0171] In a similar manner as described in Example 4-1, compounds in Example 4-2 to 4-4 as shown in Table 4 were synthesized.

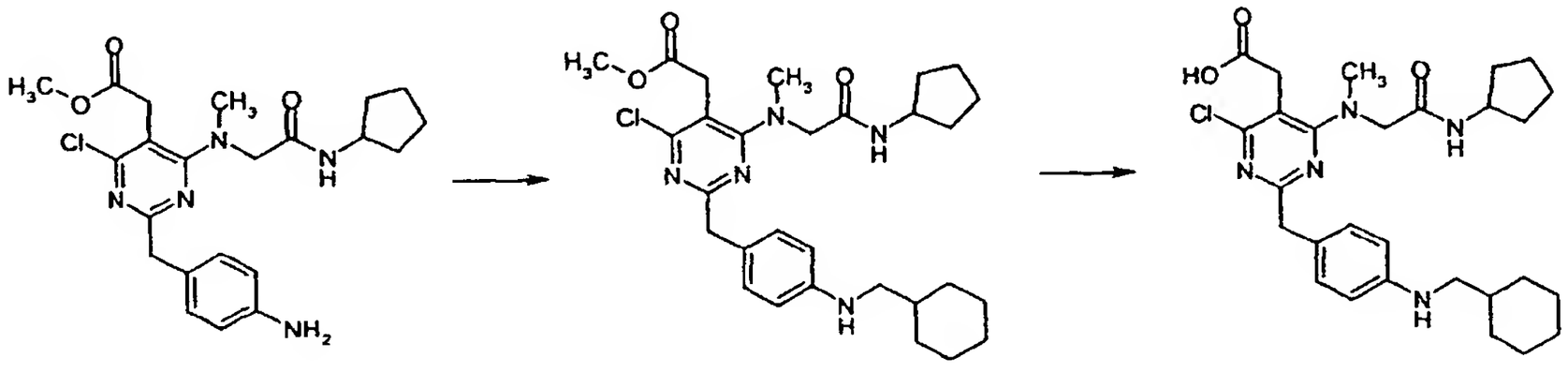
Table 4

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
4-2		565,08	564	565	>134 Z	B
4-3		579,10	578	579	>146 Z	B
4-4		601,11	600	601	>165 Z	B

Example 5-1

[4-Chloro-2-{4-[(cyclohexylmethyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl]acetic acid

[0172]



[0173] A mixture of methyl [2-(4-aminobenzyl)-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl]acetate (0.150 g, 0.336 mmol), cyclohexanecarbaldehyde (0.042 g, 0.370 mmol), acetic acid (0.019 mL, 0.336 mmol) and sodium triacetoxyborohydride (0.107 g, 0.505 mmol) in 1,2 dichloroethane (3 mL) was stirred overnight at r.t. Water was then added and the mixture was neutralized with 1N NaOH followed by extraction with dichloromethane. The combined organic extracts was washed sequentially with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product thus obtained was chromatographed by preparative TLC to give methyl [4-chloro-2-{4-[(cyclohexylmethyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl] acetate (0.092 g, 51% yield) as an amorphous solid.

[0174] A solution of methyl [4-chloro-2-{4-[(cyclohexylmethyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl]acetate (0.083 g, 0.15 mmol) in THF (5 mL) was treated with 1N NaOH (2.5 mL) and the resulting mixture was stirred at r.t. for 13 h. Subsequent to neutralization with 6N HCl, the quenched reaction mixture was evaporated to dryness and the remaining residue dissolved with EtOH. The insoluble inorganic salts were removed by filtration and the filtrate was concentrated *in vacuo*. The crude product thus obtained was purified with preparative TLC eluting with 15% EtOH in CH_2Cl_2 to give [4-chloro-2-{4-[(cyclohexylmethyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl]acetic acid (0.023 g, 28% yield) as a clear oil.

^1H NMR (300 MHz, $CDCl_3$) δ: 0.85-1.32 (m, 4H),1.48-1.95 (m, 15H), 2.80-3.05 (m, 7H), 3.73 (s, 2H), 3.89 (s, 2H), 4.01 (s, 2H), 6.51 (d, J=9 Hz, 2H), 6.69 (d, J=7 Hz, 1H), 7.13 (d, J=7 Hz, 2H)

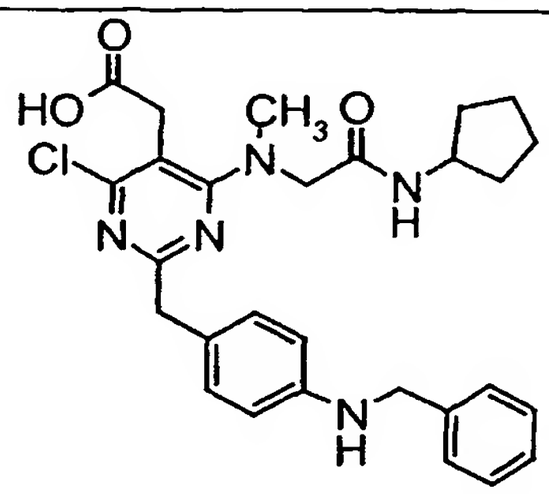
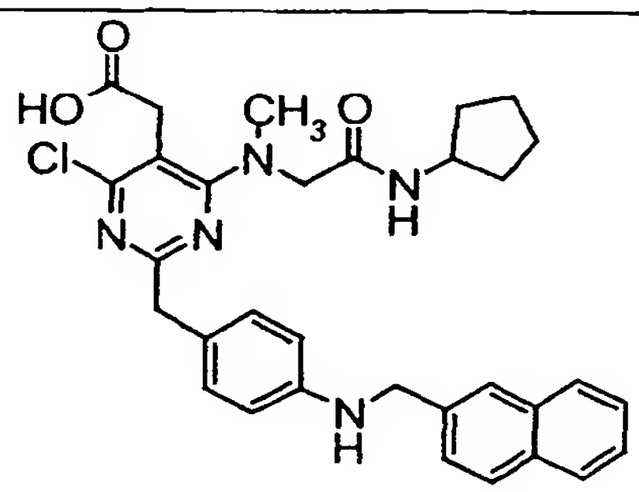
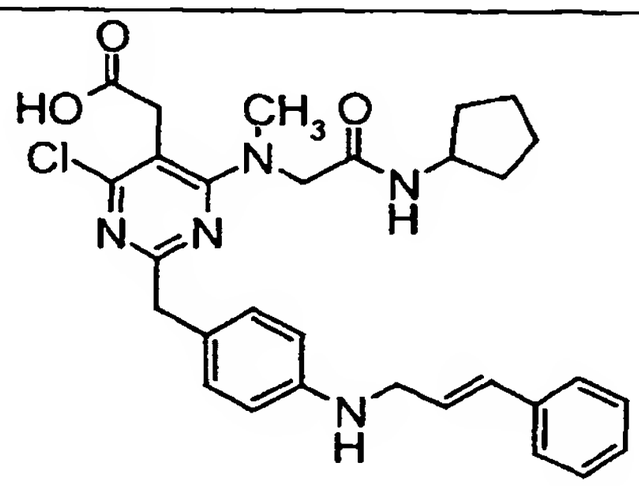
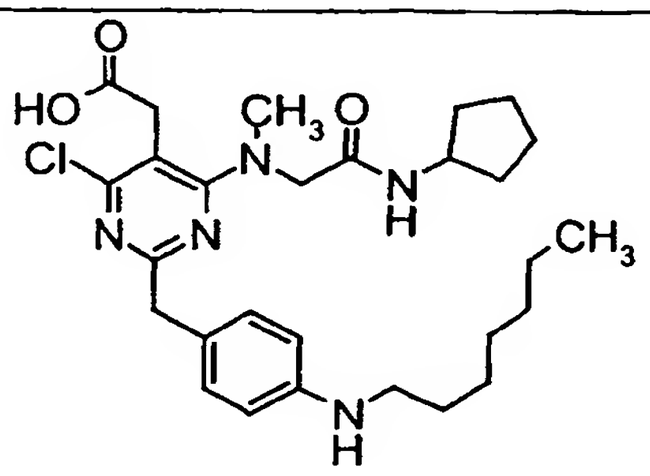
Molecular weight: 528.10

Mass spectrometry: 528

Activity class: D

[0175] In a similar manner as described in Example 5-1, compounds in Example 5-2 to 5-5 as shown in Table 5 were synthesized.

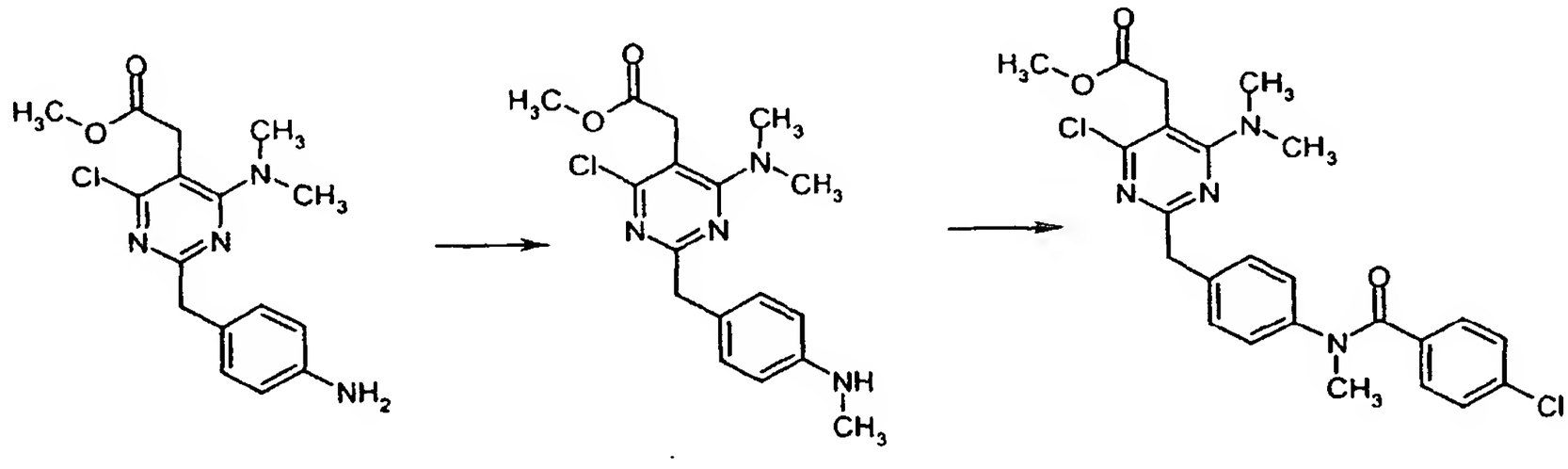
Table 5

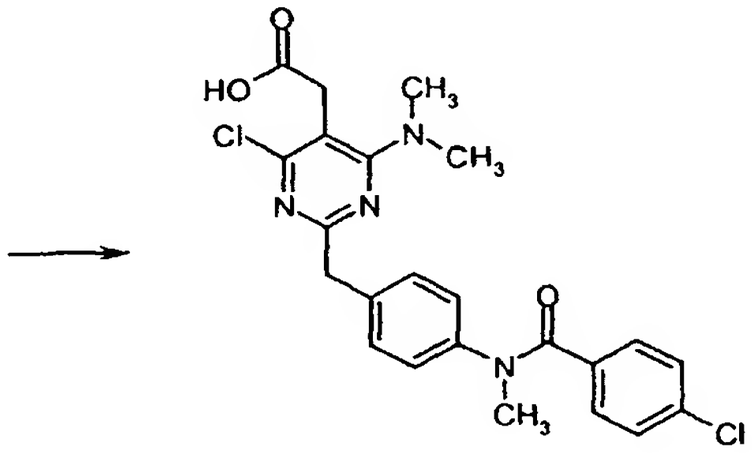
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
5-2		522,05	521	522	>70	D
5-3		572,11	571	572	>96	C
5-4		548,09	547	548	oil	C
5-5		530,12	529	530	oil	D

Example 6-1

[4-Chloro-2-{4-[(4-chlorobenzoyl)(methyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid

[0176]





[0177] To acetic anhydride (0.48 mL, 5.13 mmol) at 0 °C under Ar atmosphere was added formic acid (0.24 mL, 6.31 mmol) dropwise followed by heating of the mixture at 60 °C for 2 h. After cooling to r.t., THF (1 mL) was added followed by a solution of methyl [2-(4-aminobenzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetate (0.660 g, 1.97 mmol) in THF (1 ml). This was then stirred for 3 h and concentrated to dryness. The remaining residue was dissolved in THF and cooled to 0°C followed by the dropwise addition of borane dimethyl sulfide complex until the vigorous effervescence ceased. The mixture was gently refluxed for 14 h and then cooled to 0°C. Methanol was added and the mixture was stirred at r.t. for 1 h followed by the addition of concentrated HCl to pH ~5 and stirring was continued for another 30 min. The solvent was evaporated *in vacuo*, the remaining residue basified with water and 1N NaOH, and the aqueous layer was extracted with Et_2O. The combined organic extracts was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the crude product which was chromatographed onver silica gel eluting with 5% acetone in CH_2Cl_2 to give methyl {4-chloro-6-(dimethylamino)-2-[4-(methylamino)benzyl]-5-pyrimidinyl}acetate (0.260 g, 38% yield) as a pale yellow oil.

[0178] A solution of methyl {4-chloro-6-(dimethylamino)-2-[4-(methylamino)benzyl]-5-pyrimidinyl}acetate (0.080 g, 0.23 mmol), 1-hydroxybenzotriazole (0.043 g, 0.32 mmol), triethylamine (0.11 mL, 0.80 mmol), and 4-chlorobenzoic acid (0.043 g, 0.28 mmol) was treated with WSCI (0.066 g, 0.34 mmol) at r.t. and the reaction mixture was stirred at r.t. for 16 h. EtOAc was then added and the organic layer was washed sequentially with 0.5N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the crude product methyl [4-chloro-2-{4-[(4-chlorobenzoyl)(methyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl] acetate.

[0179] This crude methyl [4-chloro-2-{4-[(4-chlorobenzoyl)(methyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl] acetate was dissolved in THF (3 mL) and treated with 1N NaOH (2 mL) and stirred at r.t. for 24 h. Et_2O was added and the organic phase was siphoned off. The remaining aqueous layer was acidified with 6N HCl to pH~5 and the separated solids were collected by suction and rinsed with water and diisopropyl ether. Drying under high vacuum at r.t. for 4 h then gave [4-chloro-2-{4-[(4-chlorobenzoyl)(methyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid (0.029 g, 27% yield) as a pale yellow powder.

[0180] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.50 (s, 3H), 2.98 (s, 6H), 3.65 (s, 2H), 3.88 (s, 2H), 7.10 (d, J=9 Hz, 2H), 7.20 (d, J=9 Hz, 2H), 7.20-7.27 (bs, 4H), 12.77 (bs, 1H).

Molecular weight: 473.36

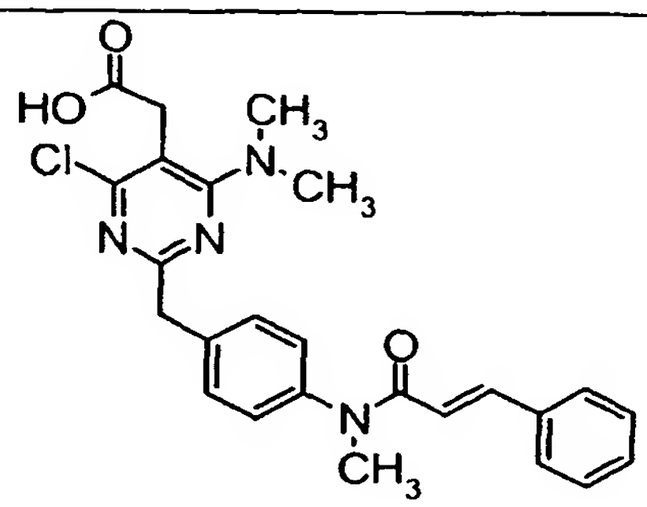
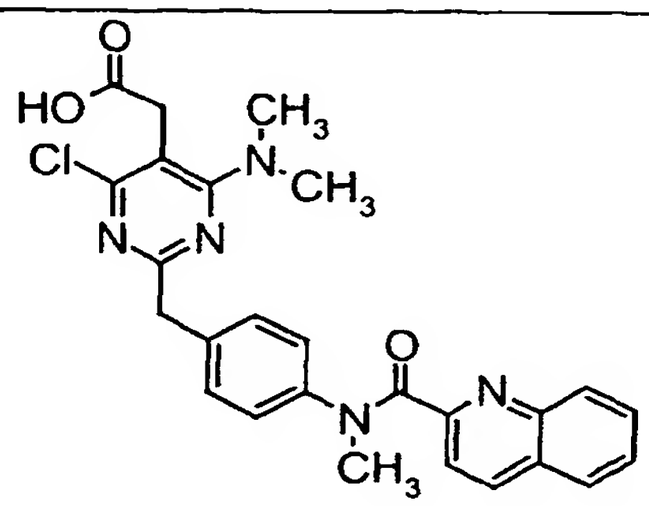
Mass spectrometry: 473

Melting point: >68 Z °C

Activity class: C

[0181] In a similar manner as described in Example 6-1, compounds in Example 6-2 to 6-3 as shown in Table 6 were synthesized.

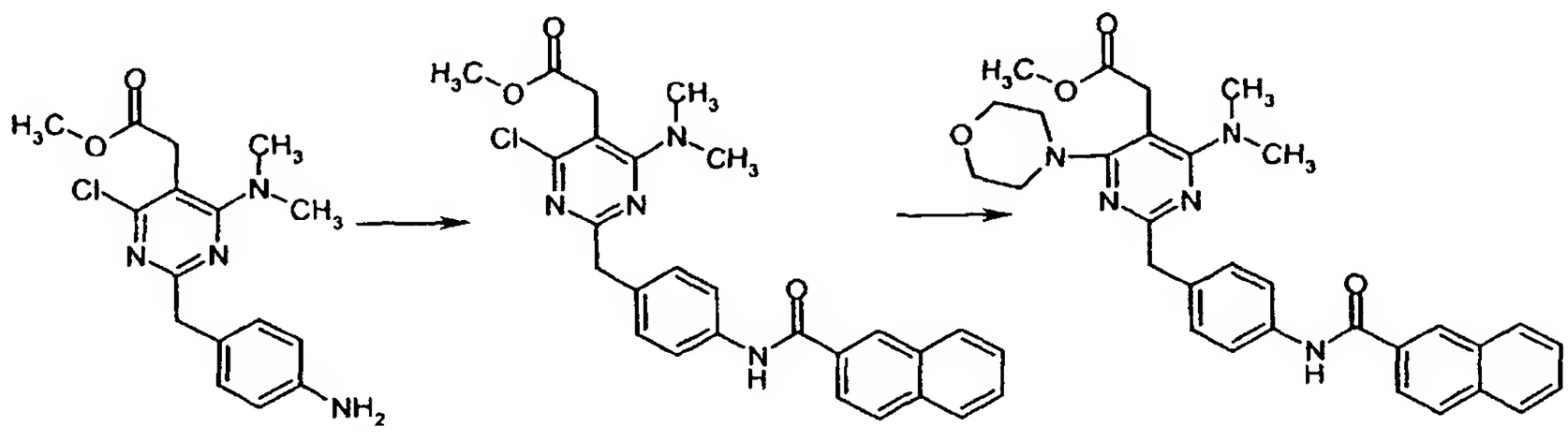
Table 6

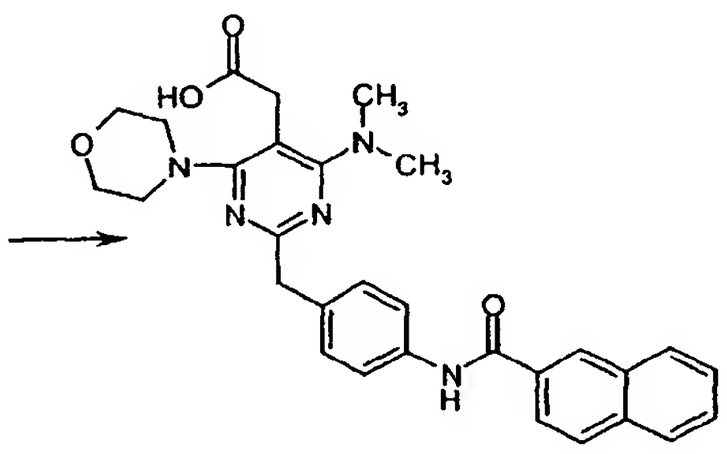
ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
6-2		464,96	464	465	80 Z	D
6-3		489,97	489	490	>78 Z	D

Example 7-1

{4-(Dimethylamino)-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid

[0182]





[0183] To a mixture of methyl [2-(4-aminobenzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetate (0.090 g, 0.30 mmol) and PyBOP (0.187 g, 0.36 mmol) in anhydrous DMF (1 mL) at r.t. was added 2-naphthoic acid (0.062 g, 0.36 mmol). The resulting reaction mixture was stirred at r.t. for 3 h at which time water was added and the resulting aqueous phase was extracted with EtOAc. The combined organic extracts was sequentially washed with 0.5N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give methyl {4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate as a colorless oil.

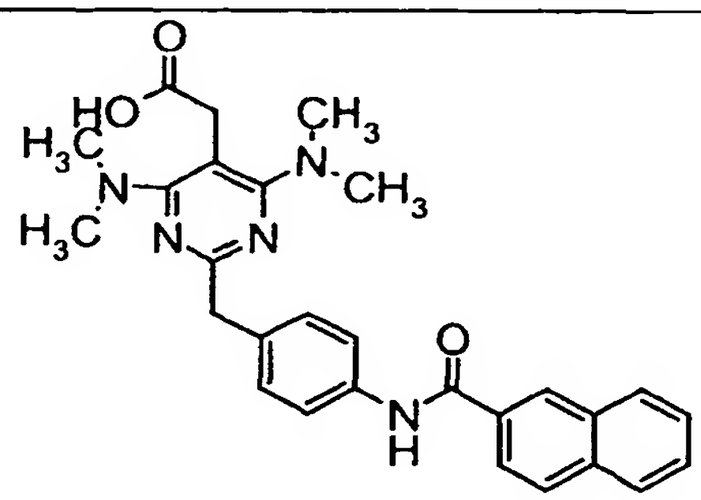
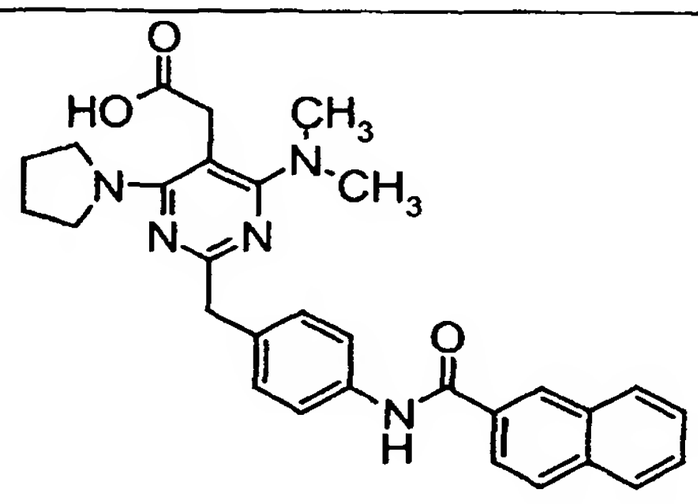
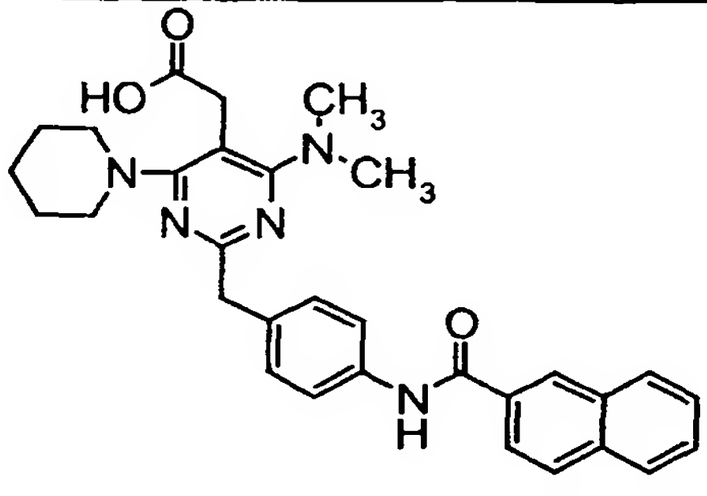
[0184] A mixture of methyl {4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl{acetate (0.094 g, 0.19 mmol) and morpholine (0.048 mL, 0.55 mmol) in DMPU (2 mL) was heated at 150 °C in a sealed tube for 15 h. After cooling to r.t., the reaction mixture was poured into water and extracted with EtOAc. The combined organic extracts was washed sequentially with 1N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. The crude product thus obtained was chromatographed over silica gel eluting with 5% EtOAc in CH_2Cl_2 to give methyl {4-(dimethylamino)-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate (0.096 g, 95% yield) as an oil.

[0185] A solution of methyl {4-(dimethylamino)-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate (0.096 g, 0.18 mmol) in MeOH (2 mL) at r.t. was treated with 1N NaOH (1 mL) and the resulting mixture was heated at 60 °C for 5 h. After cooling to r.t., the volatiles were removed under reduced pressure and the remaining aqueous layer was washed with Et_2O and acidified with 1N HCl. The separated solids were collected by suction, rinsed with water, and dried under vacuum to give {4-(dimethylamino)-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid (0.059 g, 64% yield) as a white solid.

[0186] ^1H NMR (300 MHz, DMSO-d_6) δ: 2.90 (s, 6H), 3.17 (m, 4H), 3.43 (s, 2H), 3.65 (m, 4H), 3.86 (s, 2H), 7.34 (d, J=9 Hz, 2H), 7.59-7.68 (m, 2H), 7.72 (d, J=9 Hz, 2H), 7.99-8.10 (m, 4H), 8.56 (s, 1H), 10.37 (s, 1H), 12.20 (bs, 1H)
Molecular weight: 525.61
Mass spectrometry: 526
Melting point: 218 Z °C
Activity class: B

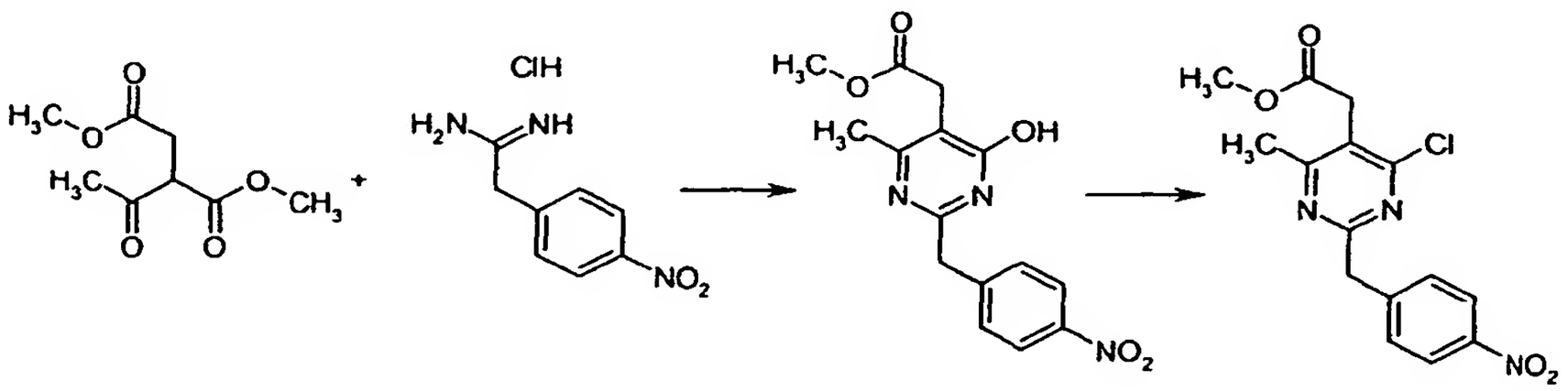
[0187] In a similar manner as described in Example 6-1, compounds in Example 7-2 to 7-4 as shown in Table 6 were synthesized.

Table 7

ex-ample No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
7-2		483,58	483	484	200 Z	B
7-3		509,61	509	510	154 Z	B
7-4		523,64	523	524	149 Z	B

Methyl [4-chloro-6-methyl-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate

[0188]



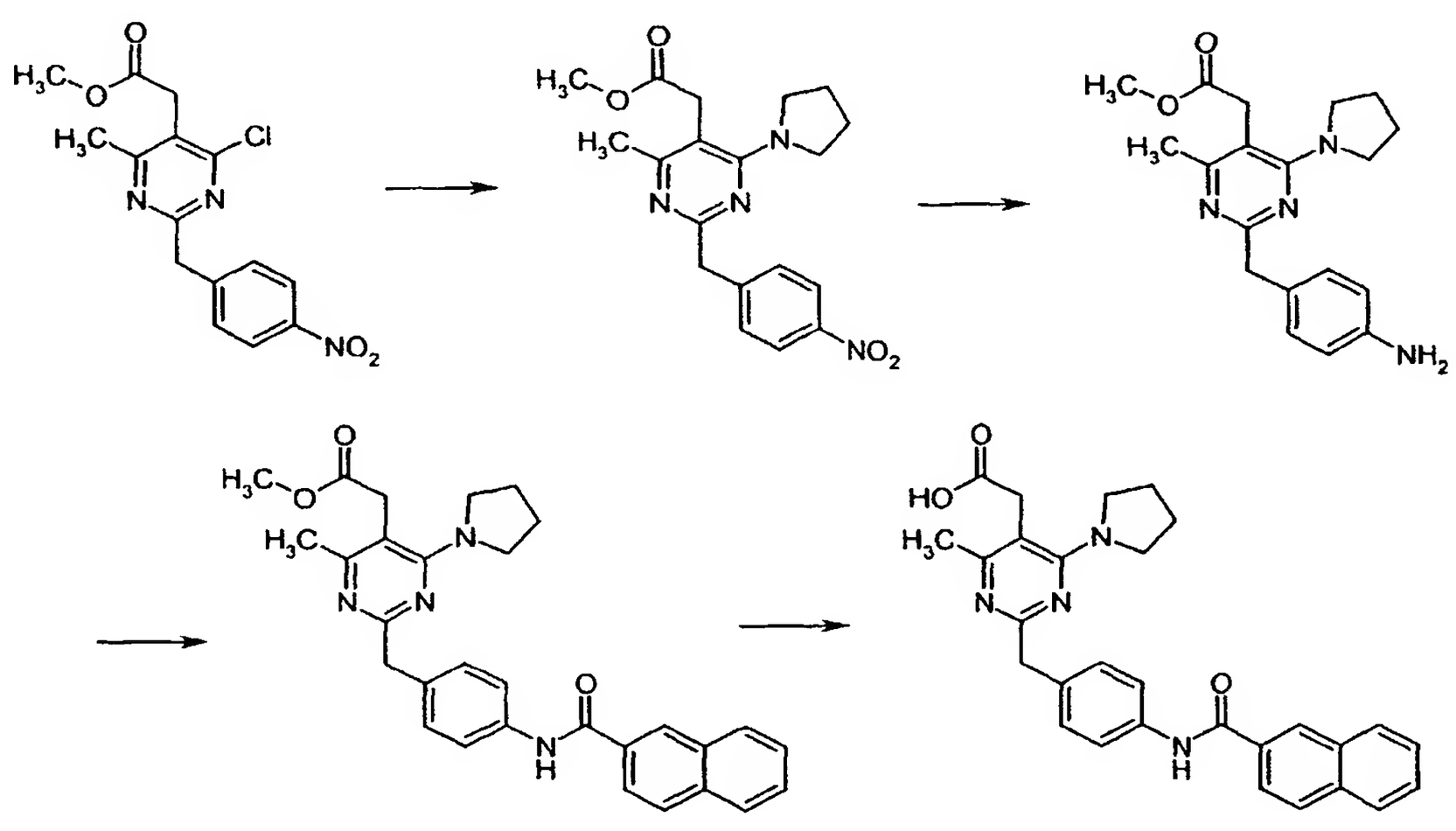
[0189] A mixture of 2-(4-nitrophenyl)ethanimidamide hydrochloride (0.22 g, 1.0 mmol), dimethyl acetylsuccinate (0.19 g, 1.0 mmol), and sodium methoxide (0.07 g, 1.3 mmol) in MeOH (10 mL) was refluxed for 15 h. After cooling to r.t., the separated solids were collected by suction and added to a pre-formed solution of thionyl chloride (0.65 mL, 8.9 mmol) in MeOH (7.5 mL). The resulting mixture was refluxed for 16 h and then cooled to r.t. Acetone was added and the precipitated solids were collected by suction, rinsed with acetone and dried under high vacuum for 4 h to give methyl [4-hydroxy-6-methyl-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (0.12 g, 38% yield) as a white solid.

[0190] A solution of methyl [4-hydroxy-6-methyl-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (1.59 g, 5.0 mmol) and *N,N*-dimethylaniline (0.56 mL, 4.4 mmol) in $POCl_3$ (2.33 mL, 25 mmol) was refluxed for 14 h. After cooling to r.t., the reaction mixture was poured into ice-cold saturated K_2CO_3. The resulting aqueous layer was extracted with EtOAc and the combined organic extracts was washed with brine, dried over anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude product thus obtained was chromatographed over silica gel eluting with 20% EtOAc in *n*-hexane to afford methyl [4-chloro-6-methyl-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (0.54 g, 32% yield) as a white powder.

Example 8-1

[4-Methyl-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid

[0191]



[0192] A solution of methyl [4-chloro-6-methyl-2-(4-nitrobenzyl)-5-pyrimidinyl]acetate (0.45 g, 1.3 mmol) and pyrrolidine (0.13 mL, 1.6 mmol) in DMF (10 mL) at r.t. was treated with triethylamine (0.22 mL, 1.6 mmol) and the resulting mixture was stirred at 85 °C for 13 h. After cooling to r.t., the reaction mixture was poured into water and extracted with EtOAc. The combined organic extracts was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product thus obtained was chromatographed over silica gel eluting with 50% EtOAc in CH_2Cl_2 to give methyl [4-methyl-2-(4-nitrobenzyl)-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.40 g, 80% yield) as a white powder.

[0193] To a solution of methyl [4-methyl-2-(4-nitrobenzyl)-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.074 g, 0.20 mmol) in anhydrous THF (2 mL) was added Pd/C (10% Pd, 0.050 g) and the resulting black suspension was stirred under an atmosphere of hydrogen. After 1 h, the reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to give methyl [2-(4-aminobenzyl)-4-methyl-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate.

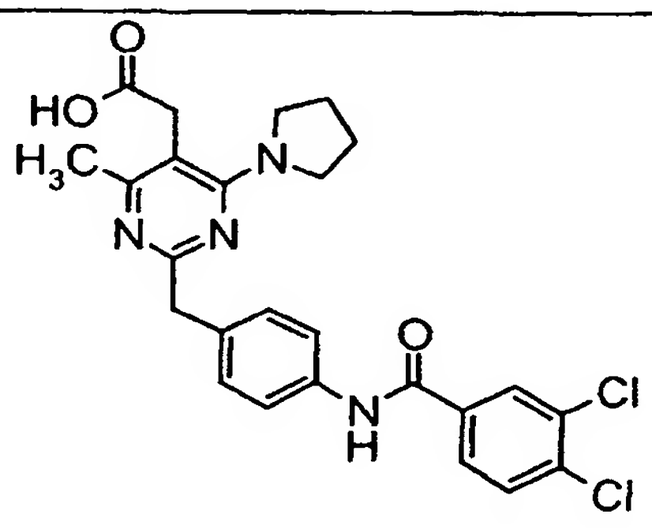
[0194] A solution of methyl [2-(4-aminobenzyl)-4-methyl-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.034 g, 0.10 mmol) in THF (1 mL) at r.t. was treated with PyBOP (0.052 g, 0.10 mmol), 2-naphthoic acid (0.019 g, 0.11 mmol), and *N,N*-diisopropylethylamine (0.017 mL, 0.10 mmol). After stirring at r.t. for 17 h, the reaction mixture was poured into water and extracted with EtOAc. The combined organic extracts was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining residue was chromatographed over silica gel eluting with 60% EtOAc in CH_2Cl_2 to give methyl [4-methyl-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.018 g, 36% yield) as a yellow oil.

[0195] A solution of methyl [4-methyl-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetate (0.018 g, 0.04 mmol) in THF (1 mL) at r.t. was treated with 1N NaOH (0.5 mL) and the resulting biphasic mixture was stirred at 60 °C for 13 h. After cooling to r.t., Et_2O was added and the organic layer siphoned off. The remaining aqueous layer was acidified with 6N HCl and the separated solids were collected by suction, rinsed with water, and dried under high vacuum for 4 h to give [4-methyl-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid (0.006 g, 37% yield) as a white solid.

[0196] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.86 (bs, 4H), 2.29 (s,3H), 3.60 (bs, 4H), 3.71 (s, 2H), 3.94 (s, 2H), 7.35 (d, J=8 Hz, 2H), 7.60-7.67 (m, 2H), 7.75 (d, J=8 Hz, 2H), 8.00-8.10 (m, 4H), 8.56 (s, 1H), 10.40 (s, 1H), 12.73 (bs, 1H)
Molecular weight: 480.57
Mass spectrometry: 481
Melting point: 184 Z °C
Activity class: A

[0197] In a similar manner as described in Example 8-1, compound in Example 8-2 as shown in Table 8 was synthesized.

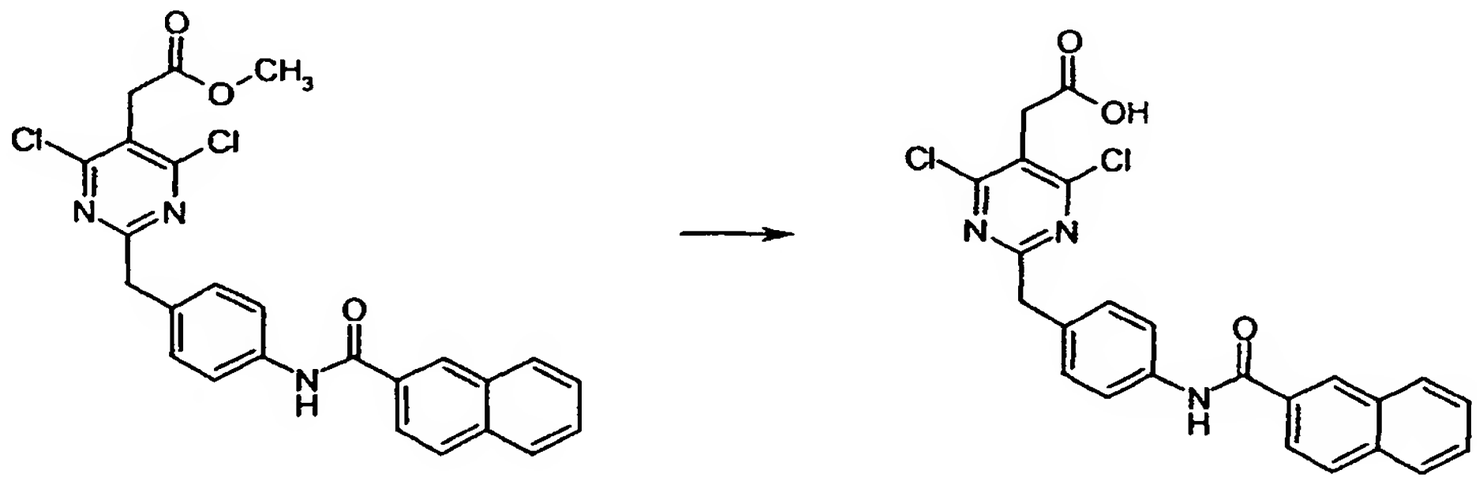
Table 8

example No	Structure	MW	Exact Mass	MS	mp (°C)	Activity class
8-2		499,40	498	499	196 Z	A

Example 9-1

{4,6-Dichloro-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid

[0198]



[0199] A THF (1.5 mL) solution of methyl {4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetate (0.048

g, 0.10 mmol) at r.t. was treated with 1N NaOH (1 mL). After stirring for 16 h at r.t., the reaction mixture was poured into water and washed with EtOAc. The aqueous layer was acidified with 1N HCl and back extracted with EtOAc. The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining residue was chromatographed over silica gel eluting with 10% THF in CH_2Cl_2 containing 0.5% AcOH to give {4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid (0.007 g, 15% yield) as a white solid.

[0200] ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.87 (s, 2H), 4.19 (s, 2H), 7.31 (d, J=9 Hz, 2H), 7.59-7.68 (m, 2H), 7.78 (d, J=9 Hz, 2H), 7.97-8.10 (m, 4H), 8.57 (s, 1H), 10.42 (s, 1H), 13.03 (bs, 1H).

Molecular weight: 466.33

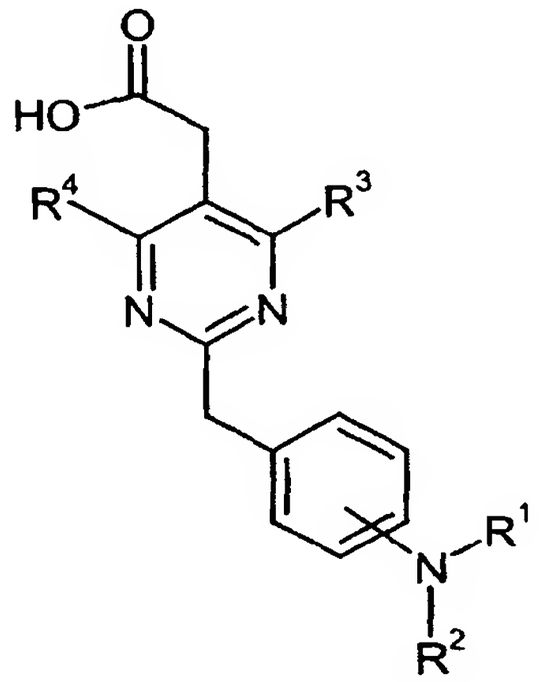
Mass spectrometry: 466

Melting point: 230 Z °C

Activity class: A

Claims

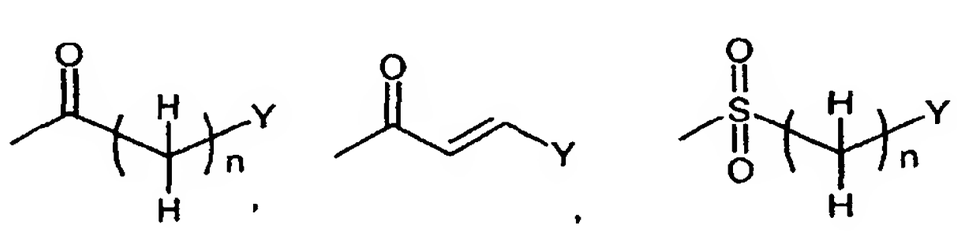
1. A pyrimidinylacetic acid derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof:

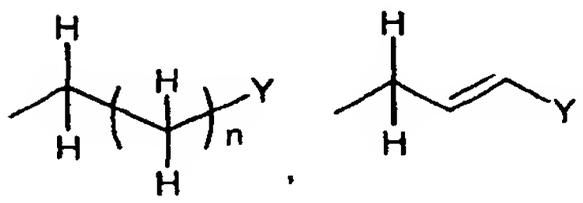


(I)

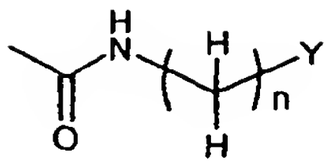
wherein

R^1 represents





or



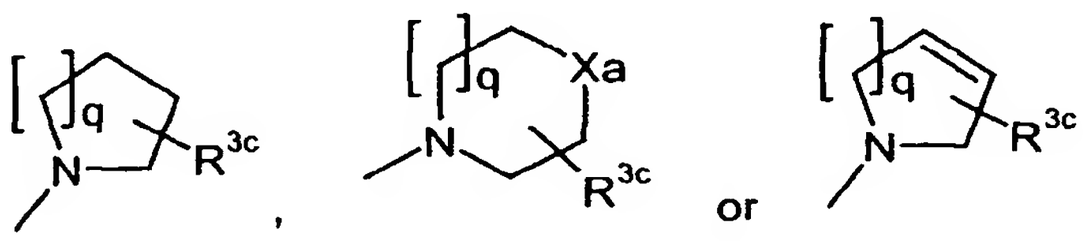
in which

n represents an integer of 0 to 6;

Y represents hydrogen, C_{3-8} cycloalkyl optionally substituted by C_{1-6} alkyl, C_{3-8} cycloalkyl fused by benzene, aryl or heteroaryl, wherein said aryl and heteroaryl are optionally substituted at a substitutable position with one or more substituents selected from the group consisting of cyano, halogen, nitro, guanidino, pyrrolyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl) aminosulfonyl, phenyloxy, phenyl, amino, C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6}alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen and C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen, or aryl fused by 1,3-dioxolane;

R^2 represents hydrogen or C_{1-6} alkyl;

R^3 represents halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen,



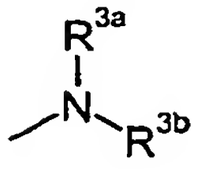
q represents an integer of 1 to 3;

R^{3c} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy or (phenyl-substituted C_{1-6} alkyl)carbamoyl;

Xa represents -O-, -S- or -N(R^{3d})-
in which

R^{3d} represents C_{1-6} alkyl;

or



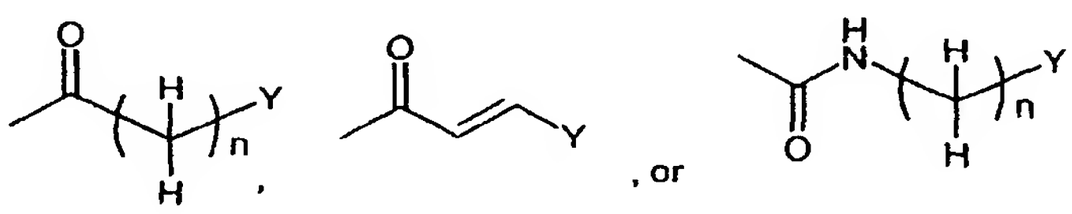
in which

R^{3a} and R^{3b} independently represent C_{3-8} cycloalkyl, or C_{1-6} alkyl optionally substituted by carboxy, C_{3-8} cycloalkyl, carbamoyl, C_{1-6} alkylcarbamoyl, aryl-substituted C_{1-6} alkylcarbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6}alkyl)carbamoyl, C_{3-8} cycloalkylcarbamoyl, C_{3-8}heterocyclocarbonyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino or C_{1-6} alkoxy; or

R^4 represents hydrogen, halogen, C_{1-6} alkoxy, di(C_{1-6} alkyl)amino or C_{1-6} alkyl optionally substituted by mono-, di-, or tri- halogen.

2. The pyrimidinylacetic acid derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,
wherein

R^1 represents



in which

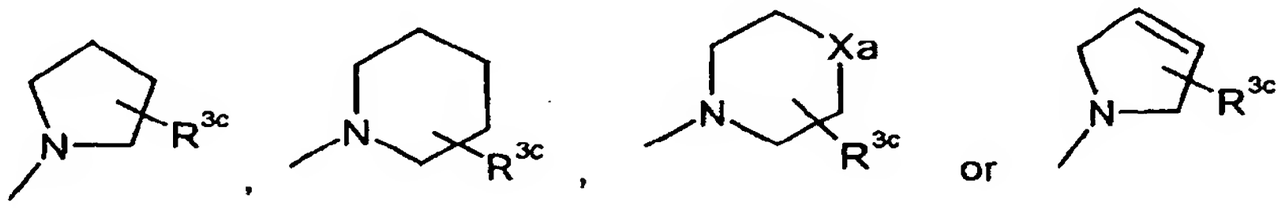
n represents an integer of 0 to 2;

Y represents C_{3-8} cycloalkyl optionally substituted by C_{1-6} alkyl, C_{3-8} cycloalkyl fused by benzene, aryl selected from the group consisting of phenyl and naphthyl, or heteroaryl selected from the group consisting of indolyl, quinolyl, benzofuranyl, furanyl and pyridyl, wherein said aryl and heteroaryl are optionally substituted at a substitutable position with one or more substituents selected from the group consisting of cyano, halogen, nitro, pyrrolyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, phenyloxy, phenyl, C_{1-6}alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkanoylamino, carbamoyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen and C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen; or

R^2 represents hydrogen.

3. The pyrimidinylacetic acid derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1,
wherein

R^3 represents C_{1-6} alkoxy optionally substituted by mono-, di-, or tri-halogen,

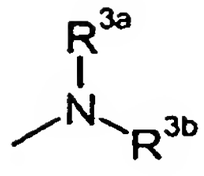


R^{3c} represents hydrogen, hydroxy, carboxy, or C_{1-6} alkyl optionally substituted by hydroxy, carboxy or (phenyl-substituted C_{1-6} alkyl)carbamoyl;

Xa or represents -O-, -S- or -N(R^{3d})-,
in which

R^{3d} represents C_{1-6} alkyl;

or



in which

R^{3a} and R^{3b} independently represent C_{1-6} alkyl optionally substituted by carboxy, C_{3-8} cycloalkyl, carbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, C_{3-8} cycloalkylcarbamoyl, C_{3-8} heterocyclocarbonyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino or C_{1-6} alkoxy.

4. The pyrimidinylacetic acid derivative of the formula (I), its tautomeric or stereoisomeric form, or a salt thereof as claimed in claim 1, wherein said phenylpiperazine derivative of the formula (I) is selected from the group consisting of:

[4-methyl-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-4-methyl-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{4,6-dichloro-2-[4-(2-naphthoylamino)benzyl]pyrimidin-5-yl}acetic acid;

{4-chloro-6-{methyl[2-oxo-2-(1-pyrrolidinyl)ethyl]amino -2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(isopropylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

{4-chloro-6-[[2-(cyclohexylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

(4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(3-phenylpropanoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

(4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(2-quinolinylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

{4-chloro-2-{4-[(4-chlorobenzoyl)amino]benzyl}-6-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl} acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(4-methoxybenzoyl)amino]benzyl} -5-pyrimidinyl} acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(4-methylbenzoyl)amino]benzyl}-5-pyrimidinyl} acetic acid;

{2-{4-[(1-benzofuran-2-ylcarbonyl)amino]benzyl}-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl} acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(1H-indol-2-ylcarbonyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

{4-chloro-2-{4-[(4-cyanobenzoyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-{4-[(2,3-dihydro-1H-inden-2-ylacetyl)amino]benzyl}-5-pyrimidinyl}acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(3-phenoxyphenyl)acetyl]amino}benzyl)-5 -pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(2-quinolinylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[4-chloro-6-(dimethylamino)-2-(4-{[(2E)-3-phenyl-2-propenoyl)amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-chlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(4-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[4-chloro-6-(dimethylamino)-2-(4-{[4-(dimethylamino)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-6-(dimethylamino)-2-(4-{[4-(trifluoromethyl)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-(4-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}benzyl)-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[2-{4-[(4-bromobenzoyl)amino]benzyl}-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(2,5-dichlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-difluorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,5-dichlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3-chlorobenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(3-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[2-(4-{[(4-tert-butylcyclohexyl)carbonyl] amino} benzyl)-4-chloro-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-phenoxybenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-isopropoxybenzoyl)amino]benzyl} -6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-6-(1-pyrrolidinyl)-2-(4-{[4-(1H-pyrrol-1-yl)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-methoxy-3-nitrobenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(4-methoxy-3,5-dimethylbenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}

acetic acid;

{4-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-{methyl[2-oxo-2-(1-pyrrolidinyl)ethyl]amino}-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

[4-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[2-{4-[(4-chlorobenzoyl)amino]benzyl}-4-(dimethylamino)-5-pyrimidinyl]acetic acid;

(4-(dimethylamino)-2-{4-[(4-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[2-{4-[(3,4-dichlorobenzoyl)amino]benzyl}-4-(dimethylamino)-5-pyrimidinyl]acetic acid;

[4-(dimethylamino)-2-(4-{[(2E)-3-phenyl-2-propenoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[2-(4-{[(2E)-3-(4-chlorophenyl)-2-propenoyl]amino}benzyl)-4-(dimethylamino)-5-pyrimidinyl] acetic acid;

[4-(dimethylamino)-2-(4-([4-(trifluoromethyl)benzoyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

[2-{4-[(4-bromobenzoyl)amino]benzyl}-4-(dimethylamino)-5-pyrimidinyl]acetic acid;

{4-chloro-6-[cyclohexyl(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

(4-chloro-6-[isopropyl(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

{4-chloro-6-[(2-methoxyethyl)(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

[4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-piperidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

(4-chloro-6-(dimethylamino)-2-{4-[(1H-indol-6-ylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

{4-chloro-6-methoxy-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

{4-chloro-6-(2,5-dihydro-1H-pyrrol-1-yl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

{4-chloro-6-[ethyl(methyl)amino]-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

{4-chloro-6-(3-hydroxy-1-pyrrolidinyl)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

[4-chloro-2-(4-{[4-(methylthio)benzoyl]amino benzyl)-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3-chloro-4-methoxybenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{2-[4-(benzoylamino)benzyl]-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-2-{4-[(cyclohexylacetyl)amino]benzyl}-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(4-methylphenyl)acetyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-(1-naphthoylamino)benzyl]-5-pyrimidinyl} acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(4-phenoxyphenyl)acetyl]amino} benzyl)-5-pyrimidinyl]acetic acid;

[4-chloro-2-{4-[(3,4-dimethoxybenzoyl)amino]benzyl}-6-(dimethylamino)-5-pyrimidinyl]acetic acid;

{4-chloro-6-(dimethylamino)-2-[3-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

[4-chloro-2-{4-[(4-nitrobenzoyl)amino]benzyl}-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[2-(4-{[4-(acetylamino)benzoyl]amino}benzyl)-4-chloro-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

{2-[4-(benzoylamino)benzyl]-4-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

(4-(dimethylamino)-2-{4-[(2-quinolinylcarbonyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

(4-(dimethylamino)-2-{4-[(3-methoxybenzoyl)amino]benzyl}-5-pyrimidinyl)acetic acid;

[2-{4-[(3-chlorobenzoyl)amino]benzyl}-4-(dimethylarnino)-5-pyrimidinyl]acetic acid;

N-{5-(carboxymethyl)-6-chloro-2-[4-(2-naphthoylamino)benzyl]-4-pyrimidinyl}-N-methylglycine;

{4-chloro-6-(diethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

1-{5-(carboxymethyl)-6-chloro-2-[4-(2-naphthoylamino)benzyl]-4-pyrimidinyl}-L-proline;

{2-{4-[(anilinocarbonyl)amino]benzyl}-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{2-(4-{[(benzylamino)carbonyl] amino}benzyl)-4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-5-pyrimidinyl}acetic acid;

{4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-[4-({[(2-phenylethyl)amino]carbonyl)amino) benzyl]-5-pyrimidinyl}acetic acid;

[4-chloro-6-[[2-(cyclopentylamino)-2-oxoethyl](methyl)amino]-2-(4-{[(2-naphthylamino)carbonyl]amino}benzyl)-5-pyrimidinyl]acetic acid;

{4,6-bis(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-5-pyrimidinyl}acetic acid;

[4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-6-(1-pyrrolidinyl)-5-pyrimidinyl]acetic acid;

[4-(dimethylamino)-2-[4-(2-naphthoylamino)benzyl]-6-(1-piperidinyl)-5-pyrimidinyl]acetic acid; and

{4-(dimethylamino)-6-(4-morpholinyl)-2-[4-(2-naphthoylamino)benzyl)-5-pyrimidinyl}acetic acid.

5. A medicament comprising the pyrimidinylacetic acid derivative, its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof as claimed in claim 1 as an active ingredient.

6. The medicament as claimed in claim 5, further comprising one or more pharmaceutically acceptable excipients.

7. The medicament as claimed in claim 5, wherein said pyrimidinylacetic acid derivative of the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a CRTH2 antagonist.

8. The medicament as claimed in claim 5 for the treatment and/or prevention of a disorder or disease associated with CRTH2 activity.

9. The medicament as claimed in claim 8, wherein said disorder or disease is selected from the group consisting of asthma, allergic rhinitis, atopic dermatitis and allergic conjuvatitis.

10. The medicament as claimed in claim 8, wherein said disorder or disease is selected from the group consisting of Churg-Strauss syndrome, sinusitis, basophilic leukemia, chronic urticaria and basophilic leukocytosis.

11. Use of a compound according to claim 1 for manufacturing a medicament for the treatment and/or prevention of a disorder or disease associated with CRTH2 activity.

12. Process for controlling a disorder or disease associated with CRTH2 activity in humans and animals by administration of a CRTH2 antagonistically effective amount of a compound according to claim 1.

RCK- 53	CRTH2	Pyrimidinylacetic Acid Derivatives
Name	Nationality	Current Home Address
Tai Wei, Ly	Canadian	329-1-211 Kodono-cho, Nara-shi, Nara-ken, 630-8441, Japan
Yuji Koriyama	Japanese	5-13-6-102 Jingu, Nara-shi, Nara-ken 630-0804 Japan
Takashi Yoshino	Japanese	1-1-17-101, Saidaiji-Nogami-cho, Nara-shi, Nara-ken 631-0833 Japan
Hiroki Sato	Japanese	4-7-4-102, Jingu, Nara-shi, Nara-ken 631-0804 Japan
Kazuho Tanaka	Japanese	15-1-301 Konyama-cho, Yamato Koriyama-shi, Nara-ken 639-1148, Japan
Hiromi Sugimoto	Japanese	4-25-2-B201 Sakuragaoka, Seika-cho, Soraku-gun,Kyoto-fu, 619-0232, Japan
Yoshihisa Manabe	Japanese	4-8-19, Suzaku, Nara-shi, Nara-ken 631-0806 Japan
Kevin Bacon	British	5-15-912, Koyo-cho Naka, Higashinada-ku, Kobe-shi, Hyogo-ken 658-0032 Japan
Klaus Urbahns	German	6-3-1-301,Kusugaoka-cho, Nada-ku, Kobe-shi, Hyogo-ken 657-0024 Japan

Signature: Date:

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 03 00 9384

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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D
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INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claim 12 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
MUNICH	4 August 2003	Wörth, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 03 00 9384

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82